The Dissertation Committee for Dawn Nicole Kim-Romo Certifies that this is the approved version of the following dissertation:

The Treatment of Unipolar Major Depression with Psychotic Features Using Combination Therapy versus Monotherapy: A Study of Adherence, Persistence, Health Care Utilization and Expenditures, and Medication-Related Adverse Events

Committee:

Karen L. Rascati, Supervisor

Susan N. Beretvas

Kentya C. Ford

Kristin M. Richards

James P. Wilson

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by

Dawn Nicole Kim-Romo, PharmD MS

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Dedication

For Anthony, who gives me unwavering love and support.

1 Corinthians 13:4-8

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"I can do all things through Christ who strengthens me." -Philippians 4:13

The Treatment of Unipolar Major Depression with Psychotic Features Using Combination Therapy versus Monotherapy: A Study of Adherence, Persistence, Health Care Utilization and Expenditures, and Medication-Related Adverse Events

Dawn Nicole Kim-Romo, PhD

The University of Texas at Austin, 2015

Supervisor: Karen L. Rascati

The purpose of the study was to assess medication adherence, medication persistence, suicide ideation/attempts, health care utilization and costs, and medication adverse events in Texas Medicaid patients with psychotic depression who utilized antidepressant monotherapy (AD cohort) or antidepressant plus second-generation antipsychotic therapy (AD/SGA cohort). Using prescription and medical records from September 2007 to December 2012, beneficiaries were included if they were aged 18-63 years, had no confounding psychiatric disorders, had a 6-month pre-index period with no antidepressants plus a 12-month post-index period, and had a diagnosis for unipolar major depressive disorder with psychotic features (ICD-9-CM 296.24 or 296.34). The index date was the first claim date for an antidepressant. All participants had at least two antidepressant claims, and those in the AD/SGA cohort also had at least two SGA claims. Study covariates included: age, race/ethnicity, gender, residence, Charlson Comorbidity Index score, tobacco use and/or dependence, and antidepressant persistence.

A total of 926 participants met study criteria (AD cohort n=510; AD/SGA n=416). Overall, the mean age (±SD), Charlson Comorbidity Index score, and

antidepressant persistence rate was 40.5 (±13.2) years, 0.6 (±1.3), and 172.3 (±130.4) days, respectively. The final sample included 66.8% females, 25.2% Caucasians, 34.9% African Americans, 36.7% Hispanics, 79.5% urban dwellers, and 19.7% with known tobacco use/dependence. The AD/SGA cohort had a 53% significantly higher likelihood of being adherent to antidepressant therapy, compared to the AD cohort ($p=0.006$). Similarly, the AD/SGA cohort had a 23% significantly lower hazard of antidepressant nonpersistence (based on persistence with a 45-day gap) ($p=0.001$). Alternatively, the AD cohort had a significantly lower rate of psychotic depression-related outpatient/emergency department visits ($p<0.001$), as well as significantly lower psychotic depression-related costs (medication, medical, and total) and all-cause medication costs ($p<0.001$). There were no differences in suicide ideation/attempts or rates of incident dyslipidemia or diabetes mellitus between cohorts. Evidence of incident extrapyramidal symptoms were rare ($n=12$).

In conclusion, the AD/SGA cohort had better outcomes associated with antidepressant adherence and persistence, and the AD cohort had lower rates of health care utilization and costs. These real-world estimates should help increase the understanding of appropriate treatment for psychotic depression.

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List of Abbreviations

- **AD** Antidepressant
- **AP** Antipsychotic
- **BDI** Beck Depression Inventory
- **BPRS** Brief Psychiatric Rating Scale
- **BRMES** Bech-Rafaelson Melancholia Scale
- **CGI** Clinical Global Impression Scale
- **DSM-I** *Diagnostic and Statistical Manual of Mental Health Disorders, First Edition*
- **DSM-II** *Diagnostic and Statistical Manual of Mental Health Disorders, Second Edition*
- **DSM-III** *Diagnostic and Statistical Manual of Mental Health Disorders, Third Edition*
- **DSM-III-R** *Diagnostic and Statistical Manual of Mental Health Disorders, Third Edition, Revised*
- **DSM-IV** *Diagnostic and Statistical Manual of Mental Health Disorders, Fourth Edition*
- **DSM-IV-TR** *Diagnostic and Statistical Manual of Mental Health Disorders, Fourth Edition-Text Revision*
- **DST** Dexamethasone Suppression Test
- **ECT** Electroconvulsive Therapy
- **EPS** Extrapyramidal Symptoms

- **FGA** First-Generation Antipsychotic
- **GAF** Global Assessment of Functioning
- **GLM** Generalized Linear Model
- **HAM-D** Hamilton Depression Rating Scale
- **HDS** Hamilton Depression Scale
- **HPA** Hypothalamic Pituitary Adrenal
- **HRS15** Hamilton Rating Scale-15
- **HRS17** Hamilton Rating Scale-17
- **HRSD** Hamilton Rating Scale for Depression
- **MADRS** Montgomery-Asberg Depression Rating Scale
- **MD-Psy** Major Depressive Disorder with Psychotic Features
- **MHRSD** Modified Hamilton Rating Scale for Depression
- **MMSE** Mini Mental Status Examination
- **PANSS** Positive and Negative Syndrome Scale
- **RCT** Randomized Controlled Trial
- **RDC** Research Diagnostic Criteria
- **SGA** Second-Generation Antipsychotic
- **SSRI** Selective Serotonin Reuptake Inhibitor
- **STOP-PD** Study of Pharmacotherapy of Psychotic Depression
- **TCA** Tricyclic Antidepressant
- **VBR** Ventricle-to-Brain Ratio

Chapter 1: Introduction and Literature Review

INTRODUCTION

I. Importance of Major Depression with Psychotic Features to Society

Major depression with psychotic features (MD-Psy), or psychotic depression, is a severe subtype of major depressive disorder characterized as depression with delusions or hallucinations.[1] MD-Psy is an important public health problem, where the prevalence rate of MD-psy among patients with a diagnosis of major depressive disorder is estimated to be as low as 15% (based on a large community sample) to as high as 45% (based on a sample of inpatient geriatric patients).[2] The incidence rate of first-episode MD-Psy is approximately 44% higher than the incidence rate of first-episode schizophrenia.[3]

MD-Psy is associated with significant morbidity and mortality and a worse clinical course compared to major depressive disorder without psychotic features.[4] Patients with MD-Psy experience longer persisting and more severe depressive episodes, higher rates of relapse, increased hospitalization, more comorbidities, and higher financial dependency compared to patients with nonpsychotic depression.[5] The risk of suicide ideation, suicide attempts, and completed suicide is also high in patients with MD-Psy, with a likelihood of committing suicide five times greater in patients with MD-Psy compared to depressed patients without delusions.[4,6-8]

Treatment guidelines and algorithms have been developed for MD-Psy.[7,9-11] However, the lack of evidence and expert consensus presents no clear treatment strategy for this disorder, and the risk of suffering and relapse is very high.[2] In order to help alleviate and further prevent poor outcomes associated with MD-Psy, it is imperative to conduct more research in this psychiatric field.

II. Epidemiology of Major Depression with Psychotic Features

Several epidemiological studies have estimated the rates of MD-Psy among patients in the general population and in psychiatric populations;[3,5,12-15] however, lower prevalence rates are commonly reported in overall populations.[5,15] For example, the National Institute of Mental Health Epidemiologic Catchment Area study estimated the lifetime prevalence rates of MD-psy and major depression without psychotic features to be very low at 0.6% and 3.8%, respectively. In other words, approximately 14.7% of all patients with major depressive disorder also had psychotic features.[5] A large epidemiological study conducted in five Western European countries utilized telephone interviewing to investigate psychiatric disorders and found that the prevalence of MD-Psy in the overall population was only 0.4% compared to 2.0% for major depression without psychotic features. Essentially, about 18.5% of patients who met the criteria for major depressive episode also reported having psychotic features.[15]

Studies utilizing psychiatric populations generally report higher rates of MD-Psy compare to overall population studies.[3,5,12-15] In a sample of community patients seeking outpatient psychiatric treatment, approximately 4.5% of patients with current diagnoses of major depression also had psychotic features, and 2.4% of the sample had a lifetime history of psychotic depression.[14] Coryell and associates[12] estimated that, over a two-year period, 25.3% of admitted patients diagnosed with major depression also presented with delusions or hallucinations. And a study utilizing a five-year period chart review of psychiatric hospital admissions estimated that 44.7% of geriatric patients diagnosed with unipolar major depression were also delusional, indicating much higher rates of MD-Psy later in life.[13] Finally, Crebbin and associates[3] conducted an epidemiological study from 1998 to 2005 assessing the incidence of both first-episode MD-Psy and first-episode schizophrenia and found a higher incidence of

MD-Psy. Out of 540 cases of first-episode psychotic illness, there were 105 new cases of MD-Psy (19.4%) compared to 73 new cases of schizophrenia (13.5%). Specifically, patients with first-episode psychosis were significantly more likely to present with MD-Psy than with schizophrenia (RR=1.44, 95% CI=1.09-1.89, $p<0.05$).

III. Classification of Major Depressive Disorder with Psychotic Features

MD-Psy represents a severe subtype of major depressive disorder, further classified under "depressive disorders" (also known as "unipolar depression") in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision* (DSM-IV-TR).[1] The clinical course of major depressive disorder is based on the occurrence of one or more major depressive episodes. A major depressive episode is indicated by symptoms that last at least two weeks, where either a depressed mood or the loss of pleasure or interest in all activities is present. A major depressive episode also requires four additional symptoms of any of the following: significant change in weight (5% gain or loss of body weight in one month) or appetite, hypersomnia or insomnia, observable psychomotor agitation or retardation, loss of energy or fatigue, feelings of worthlessness or excessive guilt, decreased ability to concentrate or think, or recurrent thoughts of death or suicide. The majority of these symptoms must be experienced nearly every day. Other symptom criteria for a major depressive episode include: not meeting the criteria for Mixed Episode; significant impairment in areas of functioning (e.g., social and occupational); not due to other medication, drug abuse, or to a general medical condition; and not due to the bereavement of a loved one that persists for two months or less.

Specifically, MD-Psy refers to the classification of "Major Depressive Disorder, Severe With Psychotic Features," which is defined by the DSM-IV-TR as a major depressive episode

with the presence either delusions or hallucinations. Delusions are defined as false beliefs held with sustained conviction despite apparent or indisputable evidence to the contrary. These beliefs are not generally accepted by others in relation to culture, subculture, or religious faith. Hallucinations are defined as sensory perceptions that occur in the absence of external stimuli but have the sense of real perception.[1]

Delusions and hallucinations can be further classified as either mood-congruent (consistent with depressed mood) or mood-incongruent (not consistent with depressed mood). Examples of mood-congruent psychotic features include: delusions of guilt, punishment, or poverty; nihilistic or somatic delusions; auditory hallucinations about inadequacies or sins. Mood-incongruent psychotic features involve delusions or hallucinations that do not typically fit the consistent themes of depression, such as persecutory delusions, delusions of thought insertion or thought broadcasting, or delusions of control.[1,16]

Because previous studies on MD-Psy used various methodologies (e.g., different definitions of MD-Psy or the inclusion of patients with bipolar disorder), discrepancies between the types and frequencies of delusions and hallucinations exist among studies. Gaudiano and associates[14] reported that the majority of their MD-psy patients presented with hallucinations compared to delusions (80% versus 32%, respectively), while other studies reported current hallucinations in 7.7% to 29.0% of MD-psy patients.[17,18] Current delusions were reported in various studies assessing MD-Psy, where somatic delusions (3.6% to 28.4%), nihilistic delusions (17.8% to 53.8%), and delusions of guilt (7.7% to 57.1%) were the most commonly occurring types.[14,17-19]

IV. Biological and Clinical Factors of Major Depression with Psychotic Features

Irregular biological processes are associated with MD-Psy relating to increased hypothalamic pituitary adrenal (HPA) axis activity, enlarged ventricle-to-brain ratios (VBRs), and decreased dopamine beta-hydroxylase activity.[20-23] Increased activation of the HPA axis in MD-Psy has been established through the use of dexamethasone suppression tests (DST), 24-hour urinary cortisol levels, and cortisol blood levels. A meta-analysis of 14 studies comparing DST results among depressed patients with and without psychotic features reported that patients with MD-Psy were significantly more likely to have higher rates of nonsuppression on the DST (OR=3.0, 95% CI=2.2-4.1, $p<0.001$). The overall rate of nonsuppression was higher for patients with MD-Psy compared to nonpsychotic depressed patients (64% and 41%, respectively).[24] A study assessing cortisol blood levels also reported increased HPA axis activity in patients with MD-Psy. Specifically, evening cortisol levels (6pm – 1am) were significantly higher in patients with psychotic depression compared to patients with nonpsychotic depression ($p<0.02$) and healthy controls ($p<0.003$).[25]

A study that found significantly higher post-dexamethasone cortisol levels in patients with unipolar psychotic depression compared to unipolar nonpsychotic patients ($p<0.05$) also reported larger VBRs and more brain atrophy in patients with unipolar psychotic depression. Psychotic depressed patients had significantly larger anterior pole and cella media VBRs (both $p<0.05$) and were significantly more likely to have cella media VBRs greater than 0.061 ($p=0.03$), compared to nonpsychotic depressed patients. Significantly more atrophy was observed in the left and right parietal lobes of the brain in patients with unipolar MD-psy, compared to patients with unipolar nonpsychotic depression (both $p<0.05$).[26]

Studies have hypothesized that dopamine, glucocorticosteroid, and serotonin pathways have an association with delusions and MD-Psy.[27-31] Meyers and associates[27] found that elderly patients with delusional depression had significantly lower dopamine beta-hydroxylase activity compared to patients with nondelusional depression ($p=0.04$) and elderly controls ($p=0.02$). Belanoff and associates[28] hypothesized that the metabolism of dopamine and delusion development was related to excessive glucocorticosteroid activations. Short-term medication trials of four or seven days with mifepristone (also known as RU486), a glucocorticosteroid antagonist, reported favorable responses and improved Hamilton Rating Scale for Depression scores (HRSD) and Brief Psychiatric Rating Scale (BPRS) scores in patients with psychotic major depression.[28,29] Finally, two Italian studies assessing selective serotonin reuptake inhibitor (SSRI) monotherapy advocated the importance of serotonergic pathways in patients with delusional depression. Both studies reported high response rates to SSRI monotherapy with 72% and 84% responding to sertraline and fluvoxamine therapy, respectively.[30,31]

The effect of biological factors on clinical features has been studied by Keller and associates,[25] where an interaction of depression and psychotic symptoms was significantly associated with a higher cortisol nadir ($p<0.02$). Rothschild and associates[26] found that neuropsychological functioning was much worse in patients with unipolar psychotic depression compared to nonpsychotic depressed patients in relation to brain atrophy and VBRs. Specifically, patients with MD-Psy performed significantly worse on the "m and n's" subtest for both the left and right hands ($p=0.022$ and $p=0.017$, respectively), indicating frontal lobe dysfunction. They also had significantly lower drawing quality test scores ($p=0.037$), which are associated with the function of both frontal and temporal lobes. Overall, patients with larger cella media VBRs performed significantly worse on the animal naming test ($p<0.01$). Larger

anterior pole VBRs were associated with significantly worse scores on immediate visual memory ($p<0.01$), immediate recall ($p<0.01$), delayed drawing quality ($p<0.05$), animal naming ($p<0.01$), blocked design ($p<0.05$), and digit span ($p<0.05$). Atrophy of the inferior parietal lobe of the brain also correlated with worse scores on immediate drawing quality recall, delayed drawing quality recall, finger tapping, the "m and n's" test, digit span, and digit symbol (all $p<0.05$).

The neuropsychological functioning of patients with MD-Psy has been reported in two other studies.[32,33] Fleming and associates[32] conducted a meta-analysis of five studies to assess the correlation between five domains of neuropsychological functioning (i.e., visual-spatial skills, psychomotor speed and dexterity, attention, memory, and executive functioning) and psychotic major depression. The authors noted that analyses of the psychomotor speed, verbal memory, and executive functioning cognitive domains had the largest standardized differences and more precise standard errors. Hill and associates[33] reported similar but less severe profiles of neuropsychological functioning in patients with psychotic depression when compared to patients with schizophrenia. Interestingly, patients with nonpsychotic depression had neuropsychological profile patterns similar to healthy individuals.

Other clinical factors linked with MD-Psy include: psychosocial impairment, a family history of mental disease, low depression scores, and poor outcomes related to depression.[4,6,14,20-23,34] Psychosocial impairment related to work, relationships, recreation, overall satisfaction, and social functioning was higher in patients with psychotic depression compared to those with nonpsychotic depression at follow-up. Social functioning was significantly worse in patients with psychotic depression at five years follow-up ($p<0.002$), and relationships with friends, recreational activities, and social functioning were significantly more impaired in these patients at 10 years follow-up ($p<0.01$, $p=0.03$, $p=0.006$, respectively).[35] Another study reported that

patients with psychotic depression had significantly higher social impairment, compared to patients with nonpsychotic depression ($p<0.001$).[34] Oppositely, significantly higher Global Assessment of Functioning (GAF) scores were reported in patients with psychotic depression, compared to patients with nonpsychotic depression.[14]

Family history of mental disease has been discussed in a few review papers on psychotic depression. The reviews find that the general lack of information and the lack of agreement among studies do not allow for a strict consensus on the role of family history in MD-Psy.[20,21,23] Naz and associates[36] determined that 53.5% of first-admission patients with major depressive disorder with psychotic features had a family history of mood disorder. A study conducted by Coryell and associates[12] found that more patients with psychotic depression had a first-degree relative that was diagnosed with schizophrenia, compared to nonpsychotic depressed patients ($p=0.016$). And a significantly larger proportion of patients with delusional depression had a family history of depression compared to non-delusional depressed patients (84.6% and 25.0%, respectively; $p<0.01$).[18] However, Gaudiano and associates[34] found that patients with psychotic depression did not have an increased likelihood of having a first-degree relative with major depression, bipolar disorder, anxiety disorder, psychotic disorder, or substance abuse disorder, compared to patients with nonpsychotic depression.

Depression scales, such as the Clinical Global Impression Scale (CGI), the Beck Depression Inventory (BDI), the Montgomery-Ashberg Depression Rating Scale (MADRS), the Brief Psychiatric Rating Scale (BPRS), and the Hamilton Depression Rating Scale (HAM-D)—also known as the Hamilton Depression Rating Scale (HDRS), the Hamilton Depression Scale (HDS), the Hamilton Rating Scale (HRS_{17} and HRS_{15}), and the Modified Hamilton Rating Scale for Depression (MHRSD), have been utilized in several studies focusing on MD-Psy, where

more severe depression was generally associated with MD-Psy.[12,14,18,36-39] Compared to patients with nonpsychotic depression, patients with psychotic depression had significantly more severe depression based on the CGI ($p<0.001$).[14] At baseline, patients with psychotic major depression had more severe depression based on MADRS, HRSD, HRS17, and HRS15, compared to patients with nonpsychotic depression ($p=0.02$, $p=0.03$, $p=0.024$, $p=0.042$, and $p<0.001$, respectively),[12,37,38] while only one study found no difference in depression severity based on the BDI.[12] A study on delusional depression showed that pre-treatment and post-treatment HDS scores were significantly worse for patients with delusional depression versus patients with non-delusional depression (both $p<0.01$).[18]

Depression-related outcomes in MD-Psy are poor, where over a four-year period the rates of partial remission and non-remission were 23.0% and 8.0%, respectively, and relapse into depression occurred in 43.3% of patients who remitted.[36] Psychotic depressed patients were significantly more likely to be younger at onset, experience episodes of longer duration, and have a higher number of past episodes of psychotic depression ($p<0.001$, $p<0.001$, and $p=0.024$, respectively).[40] Compared to nonpsychotic depressed patients, psychotic depressed patients experienced significantly more chronic depression ($p=0.002$), recurrent depression ($p=0.03$), previous episodes of depression ($p<0.001$), and previous treatment with ECT ($p=0.03$).[34,38] Patients with psychotic depression also had significantly higher suicidality (i.e., past suicide attempts, suicide ideation, thoughts of death, thoughts of suicide, or a suicide plan) (all $p<0.05$ or less) and more past hospitalizations ($p<0.001$) versus those with nonpsychotic depression.[14,34] Psychomotor agitation, indecisiveness, and insomnia were significantly higher in patients with psychotic depression compared to those with nonpsychotic depression (all $p<0.05$).[14] Also, these patients suffered from significantly worse depressed mood ($p=0.0398$), guilt ($p=0.0003$),

retardation ($p=0.0001$[12] and $p=0.002$[41]), loss of insight ($p=0.005$), depersonalization $p=0.02$), paranoia ($p=0.002$), and obsessive compulsive symptoms ($p=0.002$).[12,37,41] Correspondingly, the likelihood of being diagnosed with obsessive-compulsive disorder ($p=0.002$), posttraumatic stress disorder ($p<0.001$), somatoform disorders ($p=0.002$), and cluster A personality disorder ($p=0.008$) psychiatric comorbidities during their lifetime was significantly higher in patients with psychotic depression compared to nonpsychotic depressed patients.[34]

DIAGNOSES

I. Past and Present Diagnoses

Hamoda and Osser,[7] of the Harvard South Shore group, cite the difficulty in developing treatment algorithms for MD-Psy. The diagnosis of MD-Psy is complex, and the diagnostic criteria for this mental disorder have changed and varied over time – making it difficult to compare MD-Psy treatment outcomes associated with different diagnostic criteria.[7,21]

The American Psychiatric Association's first and second editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-I and DSM-II) did not provide explicit criteria for the diagnosis of psychiatric illnesses.[42] In 1972, the Feighner Criteria,[43] a publication on 14 different psychiatric illnesses, did not include a subcategory of psychotic depression under their criteria for "Depression." In 1978, Spitzer and associates[42] published the "Research Diagnostic Criteria" (RDC), which further elaborated on the work of the Feighner group and established 25 major diagnostic categories. Of these categories, "Psychotic, Incapacitating, and Endogenous Major Depressive Disorder" was characterized as major depression with delusions, hallucinations, or stupor (mute and unresponsive behavior).

During the 1980s, key fundamental studies on patients with major depressive disorder who presented with delusions utilized the term "delusional depression." Some of these studies may have also included patients with bipolar I or II disorder experiencing psychotic symptoms (bipolar MD-Psy), making interpretation with these studies more difficult.[7,13,44,45] The *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) was published in 1980 and utilized the term "Major Depression with Psychotic Features," and included the same psychotic symptoms as the RDC (i.e., hallucinations, delusions, stupor). In the 1987 DSM-III-R (revised edition), stupor was no longer a part of the diagnostic criteria for "Major Depression with Psychotic Features." The term "severe" was added in the fourth edition of the DSM (DSM-IV) in 1994, and the term "Major Depressive Disorder, Severe with Psychotic Features" continues to be used in the 2000 text revision also known as the DSM-IV-TR.[1,7]

Although the term "severe" is currently utilized in the DSM-IV to characterize psychotic depression, researchers warn against the sole use of the term in diagnosing patients with psychotic depression, as patients without psychotic depression (no hallucinations or delusions present) may experience more severe or worse episodes of depression compared to those with psychotic depression.[46] Also, Kamara and associates[19] support that the presence of certain delusional subtypes (i.e., somatic delusions) cannot predict a distinct subgroup of patients with MD-Psy. In 2000, Carpenter and Price[47] acknowledged the need for a valid, reliable, and widely-used instrument to help enable the proper diagnosis of psychotic depression. In 2006, Meyers and associates[48] published the *Delusional Assessment Scale* (DAS), a valid, reliable, and useful five-domain instrument for the identification and characterization of delusions. This scale was used in the Study of Pharmacotherapy of Psychotic Depression (STOP-PD), a randomized controlled trial funded by the National Institute of Mental Health focusing on the efficacy and

safety of monotherapy treatment and combination treatment with olanzapine, a newer second-generation antipsychotic.[49,50]

II. Issues with Diagnosing Major Depression with Psychotic Features

The difficulty in correctly diagnosing patients with MD-Psy is associated with several issues, such as the lack of a distinct diagnostic syndrome for psychotic depression, the low research priority for MD-Psy, the difficulty in executing MD-Psy research, and the missed diagnosis and misdiagnosis of patients by clinicians.[6,23] In 1982, Brown and associates[51] suggested the need for a distinct subtype rather than "a severe variant of major depression" for psychotic depression. Roose and associates[8] also felt that, theoretically, delusional depression should be characterized as a distinct syndrome versus a severe variant based on evidence provided by studies on delusional depression. In 1992, the need for psychotic depression as a distinct syndrome in the DSM-IV was advocated by Schatzberg and Rothschild,[4] who published a review article focusing on the clinical and biological differences between patients with psychotic depression and those with nonpsychotic depression.

The low priority given to research in the treatment of MD-Psy is compounded by the fact that many obstacles stand in the way of conducting scientific research for this psychiatric illness. The inability of obtaining informed consent due to patients' incompetence and decreased decision-making skills, as well as complications in obtaining legal informed consent, are important problems associated with research in MD-Psy. Also, study protocols and methodologies (e.g., a medication-free period before randomization) can complicate patients' clinical situations to where doctors, nurses, and family members may observe the suffering of patients imposed by research. Unfortunately, increased suffering and lack of progression may

also lead to higher study drop-out rates. Finally, licensing of treatments for only a major depressive disorder subcategory rather than a distinct syndrome is also suspected to cause a hindrance in obtaining funding for research in MD-Psy.[9]

There are many reasons for missed diagnoses in MD-Psy. Clinicians often fail to adequately diagnose psychotic depression because patients and family members may not recognize the symptoms of psychotic illnesses.[52] Sometimes, during early episodes of psychotic depression, adequate patient history is unavailable.[22] Affected patients may also choose to conceal their symptoms for fear of being stigmatized as "crazy" or become so guarded and concrete that clinicians must be very particular in the way they ask about the symptoms in order to obtain accurate patient histories. Psychotic symptoms can also occur while patients are in a dissociated state, further complicating diagnosis.[52] Also, one study attributed clinicians' general failure to recognize psychotic features in major depression as a reason for the low utilization of antipsychotics in psychotic depression.[53]

Misdiagnosis in MD-Psy occurs because differentiation among other psychiatric illnesses (e.g., schizophrenia, schizoaffective disorder, bipolar disorder, posttraumatic stress disorder, obsessive-compulsive disorder, and body dysmorphic mood disorder) can be very challenging due to clinical similarities and symptom overlap.[6,20,22] For example, one study reported that 56.3% of patients who should have been diagnosed with MD-Psy received clinical diagnoses of psychosis not otherwise specified (36.7%), schizophrenia (24.4%), other psychosis (8.1%), bipolar disorder with psychotic features (6.1%), and nonpsychotic major depression (3.5%) instead.

Furthermore, the diagnosis status of patients has been shown to change over time. Two epidemiological studies found that patients diagnosed with psychotic depression were later

diagnosed with or met the diagnosis for schizophrenia at follow-up (4.4%[3] and 10.1%[5]). At one-year follow-up, 3.3% of psychotic depressed patients met the diagnostic criteria for either bipolar I disorder or bipolar II disorder.[5] In patients who were followed for two or more years, diagnoses for 28.6% and 12.2% of psychotic depressed patients were changed to bipolar I disorder and schizoaffective disorder, respectively, and 40.8% of all study patients had a clinical diagnosis change from baseline.[54]

TREATMENT

I. Current Treatment Recommendations

The American Psychiatric Association's 2010 *Practice Guideline for the Treatment of Patients with Major Depressive Disorder,* third edition,[11] recommended electroconvulsive therapy (ECT) or combination pharmacological therapy with an antidepressant and antipsychotic as first-line therapy for patients with MD-psy. Monotherapy with either an antidepressant or antipsychotic agent is recommended after failure with first-line therapy, and lithium augmentation with combination therapy may be appropriate after partial response to treatment in patients with bipolar psychotic depression. The guidelines further support the need for maintenance treatment in major depressive disorder with psychotic features due to the high risk of recurrence.

In 1999, the Texas Medication Algorithm Project Report on the treatment of major depressive disorder with psychotic features was published. The development of the algorithm was based on clinical experience and existing research on major depressive disorder, consisting of four acute treatment stages for MD-psy. Treatment recommendations for stage 1 included combination therapy with an antipsychotic and antidepressant (tricyclic antidepressant or TCA,

SSRI, or venlafaxine) or amoxapine monotherapy. If therapy failed, treatment progressed to stage 2 (switch antidepressants in combination therapy or switch to combination therapy from amoxapine monotherapy), then stage 3 (ECT), and finally stage 4 (lithium augmentation to combination therapy). Treatment response was defined as a 50% to 75% global improvement in symptoms, where response to therapy could be achieved at any of the four stages. Once patients responded to therapy but were not yet in remission (≥75% global improvement in symptoms), they moved out of the acute phase and into the continuation phase of treatment, where tapering of medications (especially the antipsychotic agent) would begin. Treatment beyond the continuation phase proceeded into the maintenance phase, where maintenance treatment was "very strongly recommended" in patients with three or more major depressive episodes.[10]

A psychopharmacology algorithm for psychotic depression was more recently published in 2008 by the Harvard South Shore Program.[7] ECT was recommended as first-line therapy for severely ill patients based on its effectiveness. If ECT failed or was not recommended, combination treatment with an antipsychotic and antidepressant (TCA or SSRI) should be utilized first. If failure occurred, the algorithm suggested switching the antidepressant in the combination therapy, or augmenting therapy with lithium. If lithium augmentation was still not successful, ECT should be reconsidered or a trial of clozapine may be administered. Finally, if patients were not eligible for antipsychotic therapy (e.g., risk of tardive dyskinesia), TCA or SSRI monotherapy may be utilized.

A 2007 review of eight different guidelines for unipolar psychotic depression found that the British NICE guideline, the Dutch multidisciplinary guideline, and the American Psychiatric Association guideline had the highest scores in quality according to the Appraisal of Guidelines for Research & Evaluation instrument.[9] While treatment guidelines and algorithms play an

important role in clinical practice, it is important for clinicians to remember that guidelines have varying degrees of evidence-based recommendations and that guidelines should not necessarily be used as a substitute for clinical judgment.[9,10]

II. Electroconvulsive Therapy

The use of ECT is recommended by the American Psychiatric Association guideline, the Harvard South Shore Program, and the Texas Medication Algorithm Project.[7,10,11] Since the 1930s, ECT has been used in the treatment of psychiatric illness. ECT involves the inducement of seizures through electric charges measured in millicoulombs while patients are under general anesthesia. Common placements of the electrodes include the right unilateral, bilateral, and bifrontal positions of the head. During ECT, an electroencephalogram is used to monitor seizure activity and seizure duration. Depending on the severity of illness, treatment in the US typically involves a total of 6-12 treatments, where ECT is administered three times a week. Generally, maintenance pharmacotherapy is initiated after remission with ECT.[55]

Petrides and associates found the remission rate with ECT in MD-Psy to be significantly higher at 95%, compared to the 83% rate in nonpsychotic depressed patients ($p<0.01$). Also, time to remission is significantly faster in psychotic depressed patients, compared to depressed patients without psychosis ($p<0.024$).[41] A literature review conducted by Khan and associates[56] also estimated that the ECT response rate in patients with psychotic depression was much higher, compared to nonpsychotic depressed patients (79.6% versus 52.7%, respectively). In a small study, retrospective chart review found that 81.8% and 100% of patients with psychotic major depressive disorder had a "good" response to ECT only (n=9 of 11) and to ECT and antipsychotic therapy (n=1 of 1), respectively. Approximately, 18.2% (n=2 or 11) had a

"partial" response to ECT, and no patients were reported to have a "poor" response or a non-response to treatment.[57] A similar study conducted prospectively observed that 66.6% and 75.0% of psychotic depressed patients who utilized therapy had a "good" response to ECT only (n=2 of 3) and to ECT and antipsychotic agents (n=3 of 4), respectively. Only one patient (33.3%) had a "partial" response to ECT only, and one patient (25.5%) had no response to ECT and antipsychotic therapy.[58] Finally, psychotic depressed patients treated with ECT had a lower likelihood of relapse at 12 months following treatment, compared to patients with nonpsychotic depression (adjusted OR=0.18, 95% CI=0.03-0.92, p=0.04).[59]

Compared to pharmacotherapy, ECT is shown to be superior in relation to response rates and speed of response. Significantly higher response rates in psychotic depression were found with ECT compared to TCA monotherapy ($p<0.01$) in a retrospective study conducted by Brown and associates.[51] Two studies assessed TCA and antipsychotic agent combination therapy versus ECT and found that ECT had significantly higher rates of response at 86% versus 42% ($p<0.005$) and 88% versus 25% ($p=0.004$).[60,61] Patients also responded significantly better to ECT in relation to depressive symptoms (100% versus 50%, $p<0.008$) and speed of resolution (1.6 ± 0.5 weeks versus 3.4 ± 1.5 weeks, $p<0.05$) compared to TCA and antipsychotic combination therapy.[60] Finally, compared to combination treatment with perphenazine and nortriptyline, patients who underwent ECT took approximately three weeks less time to respond to treatment (4 weeks versus 7 weeks, $p=0.001$).[61]

Conversely, Mulsant and associates[62] suggested that high rates of ECT referral may be due to inadequate treatment trials with pharmacotherapy in general and with the low use or no use of antipsychotic agents. The use of ECT has been associated with high (but non-significantly different) rates of mean hospitalization stays for both psychotic (43.8 days) and nonpsychotic

depressed patients (45.1 days) ($p>0.05$).[63] While increased costs associated with treatment represent one drawback to using ECT, other disadvantages include lack of access and reimbursement, as well as adverse events associated with cognitive impairment, anterograde amnesia, retrograde amnesia, and autobiographical memory loss.[7,55]

III. Antidepressant and Antipsychotic Combination Therapy

Combination therapy is considered to be the first-line pharmacotherapy treatment in MD-Psy according to the American Psychiatric Association guidelines and to US treatment algorithms.[7,10,11] In a systematic review and meta-analysis of 10 randomized controlled trials, Farahani and Correll[64] provided support for the current guidelines. They found that combination treatment with an antidepressant and antipsychotic agent had significantly less study-defined inefficacy ($p=0.03$) and lower CGI scores ($p=0.03$), compared to antidepressant monotherapy, where CGI scores ranged from 1 (normal) to 7 (extremely ill). In addition they found that combination therapy had significantly lower study-defined inefficacy and CGI depression ratings ($p<0.0001$ and $p=0.0002$, respectively), compared to antipsychotic therapy. A Cochrane review also supports that combination therapy with an antidepressant and antipsychotic was significantly more effective than antipsychotic monotherapy (RR=1.92, 95% CI=1.32-2.80, $p=0.0007$).[65] Finally, two small studies conducted by Minter and Mandel[57,58] reported "good" responses with combination therapy antidepressants and antipsychotic agents in 100% (n=2 of 2) and 93.8% (n=15 of 16) of patients with psychotic depression based on CGI and HDRS ratings, respectively.

First-Generation Antipsychotics and Antidepressants

The use of combination therapy with haloperidol and perphenazine (first-generation antipsychotic agents) was investigated prior to the studies mentioned above.[40,44,66,67] In one study, haloperidol and amitriptyline combination therapy was compared to risperidone monotherapy for the treatment of depressive syndrome. In patients with psychotic features, those who utilized combination therapy showed significant improvement in both BPRS and BRMES (Bech-Rafaelson Melancholia Scale) total scores, compared to antipsychotic monotherapy users ($p=0.016$ and $p=0.002$, respectively).[66] Spiker and associates[44] found that patients on amitriptyline and perphenzine combination treatment had better outcomes, as shown by significantly lower final HRDS, BPRS, anxiety and agitation, and global scores compared to patients on monotherapy (perhenazine alone or amitriptyline alone) (all $p<0.05$). A 78% response rate was seen in unipolar psychotic patients utilizing fluoxetine and perphenazine combination therapy, and after tapering off perphenazine therapy following four months of combination treatment, 73% of patients remained in remission over the next 11 months.[40,67]

Second-Generation Antipsychotics and Antidepressants

STOP-PD, a double-blind randomized controlled trial, was conducted from 2002 to 2007 to assess the efficacy of olanzapine (a second-generation antipsychotic) as monotherapy or in combination with sertraline (an SSRI). The STOP-PD group observed a significantly higher likelihood of remission (OR=1.28, 95% CI=1.12-1.47, $p<0.001$) and significantly higher rates of remission (41.9% versus 23.9%, $p=0.002$) with combination therapy compared to olanzapine monotherapy (olanzapine plus placebo). Another double-blind randomized controlled trial reported significantly higher rates of response with olanzapine plus fluoxetine (an SSRI)

combination therapy versus both olanzapine monotherapy and placebo in psychotic depression (overall p=0.014). Additionally, compared to olanzapine monotherapy, combination therapy was associated with significantly more improved BPRS positive scores (p=0.038).[68] An open-label study of olanzapine and fluoxetine combination therapy in patients with psychotic major depressive disorder reported treatment effectiveness based on the observed response rates for depression, psychosis, and psychotic depression (66.7%, 59.3%, and 55.6%, respectively). The authors also reported a remission rate of 40.7% with therapy in patients with psychotic depression.[69]

Studies of antidepressant and antipsychotic combination treatment using other second-generation antipsychotic agents have been published.[70-73] A randomized double-blind trial of patients with unipolar psychotic depression reported that patients on combination therapy with venlafaxine and quetiapine had significantly better outcomes of response (risk difference=32.5, 95% CI=11.8-53.2), compared to patients on venlafaxine monotherapy. In the same study, patients on combination therapy had better remission (risk difference=20.0, 95% CI=0.5-39.6), compared to patients on imipramine therapy alone.[70] Quetiapine has also been assessed in combination therapy with citalopram (an SSRI). In an open-label study, patients diagnosed with unipolar psychotic depression had a high response rate of 71%. Also, significant improvements were observed in BPRS total scores ($p<0.001$) and in 12 BPRS subscale scores including: suspiciousness, emotional withdrawal, feelings of guilt, depressive mood, anxiety, motor retardation, unusual thought content, tension, somatic concern, conceptual disorganization, blunted affect, and excitement (all $p<0.05$ or less).[71] In another open-label study on psychotic major depression, the effectiveness of aripiprazole and escitalopram (an SSRI) combination therapy was seen, where the response rates and remission rates based on the HAM-D_{17} were

62.5% and 50.0%, respectively.[72] A case series study (n=11) analyzing combination therapy with amisulpride plus an antidepressant (citalopram or mirtazapine) reported resolution of psychotic symptoms in 100% of patients and full remission of depression in 45.5% of patients.[73]

IV. Antidepressant Monotherapy

Antidepressant monotherapy is generally not recommended as first-line therapy; however, it can be useful in the treatment of MD-Psy.[7,11] Interestingly, the same Cochrane review that found that combination therapy with an antidepressant and antipsychotic was significantly more effective than antipsychotic monotherapy (RR=1.92, 95% CI=1.32-2.80, p=0.0007) also found that combination treatment with an antidepressant and antipsychotic was not significantly more effective than antidepressant monotherapy (RR=1.44, 95% CI=0.86-2.41).[65] An open-label follow-up study found that maintaining treatment effectiveness was not significantly different between treatment groups at follow-up 22 weeks later (88% on imipramine monotherapy, 92% on venlafaxine monotherapy, and 83% on venlafaxine and quetiapine combination therapy, p=0.88).[74] No significant differences in outcomes on HAM-D, BPRS, and BPRS psychoticism scores were observed between nortriptyline (a TCA) monotherapy and combination treatment with nortriptyline and perphenazine.[75] Another study reported no significant difference in treatment response based on HRSD and BPRS scores between unipolar psychotic depressed patients taking amoxapine monotherapy or combination therapy with amitriptyline and perphenazine ($p<0.10$).[76] Meyers and associates[77] reported a non-significant difference in relapse rates in patients with delusional depression who were using antidepressant monotherapy (nortriptyline or sertraline) and combination therapy (either antidepressant plus perphenazine) (15.4% versus 33.3%, respectively, p=0.40).

Antidepressant monotherapy has been shown to be efficacious in one US study and in three Italian studies.[17,30,31,40] In the US study, Rothschild and Duval[40] assessed psychotic depression at one year follow-up and found that 26 of 27 patients maintained remission on monotherapy with fluoxetine. The three Italian studies assessed patients with delusional depression, where patients with bipolar disorder with psychotic features were also included. The first study (n=59) published in March 1996, reported an 84.2% recovery rate in patients utilizing fluvoxamine monotherapy, as well as significant decreases in episodic duration, final HDRS scores, and final delusion scores (all $p<0.001$). The second study was published in December 1996 and found an intent-to-treat response rate in unipolar patients taking paroxetine and sertraline at 21% (3 out of 14) and 72% (13 out of 18), respectively. In the third study published in 2000, a non-significant difference in response rates were observed for patients taking fluvoxamine (n=14) and venlafaxine (n=12) treatment (78.6% and 58.3%, respectively, $p=0.40$).[17,30,31]

There is evidence that antidepressant monotherapy is not superior to combination therapy with an antidepressant and antipsychotic,[44,64,70] and other studies have cited poor outcomes associated with antidepressant monotherapy. Specifically, two studies by Minter and Mandel[57,58] reported high rates of poor response (73% to 100% of no response) with TCA monotherapy in the treatment of psychotic depression, and significantly higher rates of poor response to TCA therapy occurred in patients with psychotic depression versus those with nonpsychotic depression (56% versus 19%, $p=0.003$).[78] Another study cited a significant difference in response rates in psychotic and nonpsychotic depressed patients taking TCA monotherapy, where better outcomes favored depressed patients without psychosis ($p<0.01$).[51] A literature review of 26 studies estimated the overall response rate to be much lower in psychotic patients

versus nonpsychotic patients on TCA therapy (35% versus 60%).[56] And a significantly lower proportion of patients with delusional depression reached full recovery with TCA treatment, compared to the proportion of non-delusional depressed patients (15.4% versus 58.3%, $p<0.05$).[18] Oppositely, Bruijn and associates[37] assessed the effectiveness of imipramine therapy and observed that more patients with psychotic depression reached remission compared to those with nonpsychotic depression (61.5% versus 28.1%, $p=0.048$). However, this study specifically included patients diagnosed with mood-congruent psychotic features.

V. Antipsychotic Monotherapy

The use of antipsychotic monotherapy is deemed inappropriate in the treatment of MD-Psy, and results in the literature are generally not positive.[65] Several studies provide evidence of worse outcomes associated with antipsychotic monotherapy compared to combination therapy.[44,49,64,66,68] The STOP-PD study group found olanzapine monotherapy to be a significant predictor of treatment non-completion ($p=0.003$).[79] Also, not utilizing antipsychotic medication during the six-month to 12-month follow-up period was significantly associated with achieving full remission (OR=0.70, 95% CI=0.07-0.65, $p<0.01$).[80] However, a pooled study on two double-blind randomized trials found that olanzapine monotherapy was superior to placebo therapy in patients with major depression with psychotic features based on CGI scores for depression, psychosis and overall illness ($p=0.044$, $p=0.025$, and $p=0.043$, respectively) in the first trial. Oppositely, in the second trial, no significant differences between cohorts on any measures were reported in the pooled study.[68]

Table 1.1 provides a summary of the MD-Psy studies found in the literature.

Table 1.1: Summary of MD-Psy Studies: Combination Therapy, Antidepressant Monotherapy, Antipsychotic Monotherapy

Authors (Year)	Study Medications	Study Design	Sample Size/ Description	Study Outcomes Measured	Study Results
Systematic Review/Meta-Analysis					
Wijkstra et al. (2005)	AD+AP combo AD alone AP alone	10 RCTs Cochrane Review	548 patients with unipolar major depression with psychotic features based on RDC, DSM-III, DSM-IV	Efficacy as measured as a reduction of at least 50% on the HRSD, MADRS, CGI Secondary: remission, quality of life, harm	No significant difference in efficacy between AD+AP and AD alone (2 RCTs; RR=1.44, 95% CI=0.86-2.41) AD+AP more effective than AP alone (3 RCTs; RR=1.92, 95% CI=1.32-2.80)
Farahani et al. (2012)	AD+AP combo AD alone AP alone	8 RCTs Meta-Analysis	762 patients with psychotic depression based on RDC, DSM-III, DSM-IV, ICD-10	Efficacy: HRSD, BPRS, CGI Secondary: all-cause discontinuation, psychopathology ratings, side effects	AD+AP less inefficacy than AD alone (6 RCTs; RR=0.76, 95% CI=0.59-0.98) AD+AP less inefficacy than AP alone (4 RCTs; RR=0.73, 95% CI=0.63-0.84)
Randomized Controlled Trials					
Wijkstra et al. (2010)	SGA+AD AD alone	RCT, 5-year	122 patients (mean 51.6±9.6 yrs) with psychotic depression based on DSM-IV and HAM-D ≥ 18	Efficacy: HAM-D Secondary: CGI, remission based on HAM-D	Venlafaxine + quetiapine > venlafaxine (risk diff=32.5, 95% CI=11.8-53.2) No significant differences between: venlafaxine + quetiapine vs. imipramine; imipramine vs. venlafaxine
Meyers et al. (2009)	SGA+AD SGA alone	RCT, 12-week "STOP-PD study"	259 patients (mean 58.0±17.7 yrs) with unipolar psychotic depression based on DSM-IV-TR	Efficacy: Remission based on HAM-D score of ≤10	Olanzapine + sertraline had a higher remission rate than olanzapine alone (RR=1.12, 95% CI=1.12-1.47)

Table 1.1: Summary of MD-Psy Studies: Combination Therapy, Antidepressant Monotherapy, Antipsychotic Monotherapy (continued)

Authors (Year)	Study Medications	Study Design	Sample Size/ Description	Study Outcomes Measured	Study Results
Meyers et al. (2001)	FGA+AD AD alone	RCT, 26-week	28 patients (mean 71.8±8.4 yrs) with psychotic depression with delusions based on DSM-IV, post-ECT	Efficacy: Relapse based on DSM-IV criteria for delusional ideation	No significant difference in relapse between nortriptyline + perphenazine and perphenazine alone (33% combo versus 15% AD alone, Fischer's exact test p=0.40)
Muller-Siecheneder et al. (1998)	FGA+AD SGA alone	RCT, 6-week Multicenter	123 patients (19-63 yrs) with depressive and psychotic symptoms based on DSM-III	Efficacy: PANSS, BPRS	Haloperidol + amitriptyline significantly larger reductions in scale scores vs. risperidone ($p<0.01$) Included patients with schizoaffective disorder, major depression with psychotic features, nonresidual schizophrenia
Gatti et al. (1996)	AD alone	RCT, 6-week Italy	59 patients (mean 50.0±10.9 yrs) with unipolar and bipolar psychotic depression based on DSM-III-R	Efficacy: HRSD	Response rate=84.2% with fluvoxamine treatment Included bipolar psychotic depression
Prospective Studies					
Wijkstra et al. (2010)	SGA+AD AD alone	Open-label, follow-up, 4-month	59 patients (18-65 yrs) with psychotic depression based on DSM-IV and HAM-D ≥ 18	Efficacy: HAM-D	If treatment during acute phase was effective, it remained effective during 4-month continuation treatment

Table 1.1: Summary of MD-Psy Studies: Combination Therapy, Antidepressant Monotherapy, Antipsychotic Monotherapy (continued)

Authors (Year)	Study Medications	Study Design	Sample Size/ Description	Study Outcomes Measured	Study Results
Matthews et al. (2009)	SGA+AD	Open-label, 7-week	16 patients (mean 41.8±12.9 yrs) with major depression with psychotic features based on DSM-IV	Efficacy: HRSD, psychotic mood modules Secondary: EPS	Response rate=62.5%; Remission rate=50.0% while on aripiprazole + escitalopram treatment
Politis et al. (2008)	SGA+AD	Prospective, case series, 5-week	45 patients (65-87 yrs) with unipolar depression and mood-congruent psychotic symptoms based on DSM-IV	Efficacy: HDRS Secondary: EPS	Full remission of depression = 45.4%; Resolution of psychotic symptoms = 100% of patients while on amisulpride + citalopram or mirtazapine
Craig et al. (2007)	AD+AP combo AD alone AP alone	Prospective, self-reported The Suffolk County Mental Health Project	87 patients (15 to ≥30 yrs) with major depressive disorder with psychotic features based on on DSM-III	Medication use at discharge, 6 months, 24 months Percent time of use at discharge-6 months, 6-24 months	Medication use at 24 months: AD+AP = 19 (21.8%) AD therapy = 10 (11.5%) AP therapy = 5 (5.8%) ≥75% time of use 6-24 months: AD+AP = Not provided AD therapy = 24 (31.4%) AP therapy = 21 (24.4%)
Konstantinidis et al. (2007)	SGA+AD	Open-label, 6-week Multicenter	24 patients (mean 51.4±14.2 yrs) with unipolar psychotic depression based on DSM-IV, ICD-10	Efficacy: HRSD Secondary: BPRS, CGI, adverse events	Combination treatment with quetiapine and citalopram was effective and well-tolerated

Table 1.1: Summary of MD-Psy Studies: Combination Therapy, Antidepressant Monotherapy, Antipsychotic Monotherapy (continued)

Authors (Year)	Study Medications	Study Design	Sample Size/ Description	Study Outcomes Measured	Study Results
Goto et al. (2006)	SGA+AD SGA+mood stabilizers SGA alone	Prospective	20 patients (mean 54±18 yrs) with major depression with psychotic features or bipolar I disorder based on DSM-IV	Efficacy: HAM-D, PANSS	Response rate=55% after adding risperidone alone or with pre-existing AD or mood stabilizers Included patients with bipolar I disorder
Rothschild et al. (2003)	FGA+AD	Prospective, 5-week and 3-month study	40 patients (mean 42.4±11.7 yrs) with major depression with psychotic features based on DSM-III	Efficacy: HAM-D Relapse: DSM-IV, HAM-D, presence of psychotic symptoms	Response rate=30/40 study patients at 5 weeks while on fluoxetine + perphenazine After perphenazine taper following 4 months, 73% showed no signs of relapse over next 11 months
Grunze et al. (2002)	FGA+AD AD alone	Prospective, open-label, 4-week	20 patients (age not provided) with severe depression with psychotic features based on ICD-10	Efficacy: HAM-D	HAM-D response: 8/10 for nefazodone, 6/10 for amitriptyline + haloperidol Included patients with bipolar diagnosis
Matthews et al. (2002)	SGA+AD	Open-label, 6-week	27 patients (mean 41.2±14.7 yrs) with major depression with psychotic features based on DSM-IV	Efficacy: HRSD, psychotic mood modules	Depression response rate=66.7%; Psychosis response rate=59.3%; Psychotic depression response rate=55.6%; Psychotic depression remission rate=40.7% while on olanzapine + fluoxetine treatment

Table 1.1: Summary of MD-Psy Studies: Combination Therapy, Antidepressant Monotherapy, Antipsychotic Monotherapy (continued)

Authors (Year)	Study Medications	Study Design	Sample Size/ Description	Study Outcomes Measured	Study Results
Rothschild et al. (1993)	FGA+AD (+/- Lithium)	Prospective, 5-week study	30 patients (mean 37±11 yrs) with major depression with psychotic features based on DSM-III	Efficacy: HAM-D, BPRS Secondary: side effects	Response rate=78% in the 23 unipolar patients while on fluoxetine + perphenazine Included bipolar psychotic depression
Minter et al. (1979)	AD+AP ECT+AP AD alone AP alone ECT alone	Prospective	11 patients (age not provided) with depression with psychotic symptoms based on RDC	Efficacy: HDRS, CGI	"Good" response: AD+AP = 2/2 ECT+AP = 3/4 AD alone = 0/3 AP alone = 2/4 ECT alone = 2/3
Retrospective Studies					
Grunze et al. (2002)	FGA+AD AD alone	Retrospective, chart review	20 patients (47±8.2 and 49.2±7.5 yrs) with documentation of psychotic depression	Efficacy: CGI	CGI response: 6/10 for nefazodone monotherapy, 7/10 for amitriptyline + haloperidol Included patients with bipolar diagnosis
Rothschild et al. (1999)	SGA+therapy AP+therapy	Retrospective, matched	30 patients (mean 36.9±10.1 and 35.0±8.2 yrs) with major depression with psychotic features or bipolar I disorder based on DSM-IV	Favorable response defined as "much" or "very much" improvement	Favorable response rate=73% (8/11) with olanzapine vs. 27% (3/11) with other AP in of unipolar patients (p=0.043) Includes patients with bipolar I disorder

Table 1.1: Summary of MD-Psy Studies: Combination Therapy, Antidepressant Monotherapy, Antipsychotic Monotherapy (continued)

Authors (Year)	Study Medications	Study Design	Sample Size/ Description	Study Outcomes Measured	Study Results
Minter et al. (1979)	AD+AP ECT+AP AD alone AP alone ECT alone	Retrospective, chart review	54 patients (mean 41.3 yrs; no SD) with depression with psychotic symptoms based on RDC	Response: "good" based on remission of all symptoms and return to premorbid functioning	"Good" response: AD+AP = 15/16 ECT+AP = 1/1 AD alone = 2/11 AP alone = 10/15 ECT alone = 9/11

AD=Antidepressant; AP=Antipsychotic; CGI=Clinical Global Impression Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; EPS=Extrapyramidal Symptoms; FGA=First-Generation Antipsychotic; HAM-D=Hamilton Depression Scale; HRSD=Hamilton Rating Scale for Depression; MADRS=Montgomery Asberg Depression Rating Scale; PANSS=Positive and Negative Syndrome Scale; RCT=Randomized Controlled Trial; RDC=Research Diagnostic Criteria; SGA=Second-Generation Antipsychotic

VI. Other Medication Therapy

The American Psychiatric Association guidelines for major depressive disorder and the algorithm for psychotic depression by the Harvard South Shore Program recommend lithium augmentation after failure with combination therapy with an antidepressant and antipsychotic.[7,11] The Harvard algorithm also recommends the use of clozapine based on a few case reports and case series.[7] Pharmacological therapy with psychotherapy is also a treatment option suggested by the American Psychiatric Association.[11] Other treatment options that have been used in psychotic depression involve carbamazepine augmentation and short-term mifepristone therapy, but these are not currently recommended by treatment guidelines.[16,22]

Lithium augmentation is a strategy used when partial response occurs during the treatment of MD-Psy; however there remains insufficient evidence on this augmentation strategy.[23] Two studies assessing lithium augmentation in psychotic depression found that patients with bipolar psychotic depression improved with lithium, perphenzine, and fluoxetine treatment (100%, n=3) and with TCA-lithium combination therapy (100%, n=7)[67,81] In an open-label study, published in 2009, focusing on patients with unipolar psychotic depression in the Netherlands, patients were randomized 1:1:1 to treatment with imipramine, venlafaxine, or quetiapine plus venlafaxine. Patients failing to respond to treatment after seven weeks received lithium augmentation, and after four weeks of treatment, a 60% response remission rate was observed, where all patients sustained remission during follow-up.[82]

Case reports have provided some evidence of the effectiveness of clozapine in MD-Psy.[7] Dassa and associates[83] published a case report on a 40-year-old female with a history of failed treatment for psychotic depression who was started on clozapine (up to 500 mg per day) and showed improvement in psychotic features (delusions, hallucinations) within 20 days of use.

Similarly, Ranjan and Meltzer[84] reported well-tolerated and effective treatment with clozapine in three patients with psychotic depression.

There is very little published information on the use of psychotherapy in MD-Psy.[39,85] Gaudiano and associates[85] reported the benefits of using psychotherapy in patients with psychotic major depression by comparing usual care to usual care with Acceptance and Commitment Therapy (ACT). Compared to patients who only received usual care, patients who utilized ACT had significant improvement at discharge in BPRS total scores and hallucination self-ratings (frequency, believability, and distress) (both $p<0.05$). However, compared to nonpsychotic depressed patients, patients with psychotic depression had significantly poorer outcomes with combined pharmacotherapy and psychotherapy treatment. Psychotic depressed patients had significantly higher MHRSD depression scores at post-outpatient treatment and at follow-up six months later (both $p<0.05$). Also, psychotic depressed patients were four times more likely to have high symptom severity and display suicide ideation after combined pharmacotherapy and psychotherapy treatment.[39]

HEALTH OUTCOMES

I. Medication Adherence and Continued Treatment

Little is known about medication adherence in MD-Psy.[79] One study measured medication adherence as a percentage of time used at discharge and follow-up using three cut-off points (0-24%, 25-74%, and 75-100%).[80] Specifically, 31.4% and 24.4% of patients with MD-Psy reported regular use (≥75% of the time) of their antidepressant and antipsychotic medications, respectively, at follow-up 6-24 months later; however, 30.2% of the study patients reported no use of any medication during that period. Interestingly, the same study reported

patients that regularly used antidepressants at discharge to six months follow-up had an increased likelihood of regular use at 6-24 months follow-up (OR=11.08, 95% CI=3.79-32.37, p<0.001).

A follow-up study assessed adherence to medication treatment during clinical trials in the 45.2% of subjects who failed to complete the STOP-PD trial. Inpatient status at trial entry, olanzapine monotherapy, and higher total scores on the cumulative medical burden significantly predicted overall non-completion of the STOP-PD trial. Inadequate efficacy and poor tolerability were also found to be significant predictors of non-completion.[79]

There is a lack of consensus on how long to continue maintenance treatment in MD-Psy due to the absence of published data.[2,86] Often the need to weigh the risks and benefits of treatment are taken into consideration, especially with antipsychotic agents and their potential adverse events (e.g., extrapyramidal symptoms).[77,86,87] Even with only three months of life exposure to a first-generation antipsychotic agent, the risk of developing tardive dyskinesia can increase.[87] Compounding the situation, some studies support the need for continued antipsychotic use months after remission in order to decrease the rates of relapse, where 41.8% and 26.5% of cases of relapse occurred during medication-free periods and during tapering or two months after tapering off antipsychotic therapy.[38,88]

Wijkstra and associates[74] reported that continuation treatment with the therapy that was effective during acute treatment continued to be effective during a four-month follow-up period, whether it was monotherapy or combination therapy. Rothschild and Duval[40] suggested that treatment for psychotic depression with an antipsychotic medication was not required for more than four months. A review article found that clinicians generally discontinued antipsychotic medication after 4-9 months while continuing antidepressant therapy.[2] The Texas Medication

Algorithm Project recommends discontinuing an acute phase antipsychotic slowly after one to two months of use during the continuation phase.[10]

II. Suicide: Ideation, Attempts, and Completion

MD-Psy is associated with significant morbidity and mortality partly due to the high risk of suicide ideation, suicide attempts, and completed suicide.[4,6,7] A large study funded by the National Institute of Mental Health reported that patients with MD-Psy had significantly higher rates of suicidality in relation to thoughts of death ($p<0.001$), thoughts of suicide ($p<0.001$), suicide plans ($p=.01$), and suicide attempts ($p=.002$), compared to nonpsychotic depressed patients.[14] Compared to patients with nonpsychotic depression, patients with psychotic depression were significantly more likely to have attempted suicide during their lifetime (26.9% versus 39.1%, $p=0.042$) and have had suicidal ideation ($p=0.031$).[46] Similarly, Gaudiano and associates[34] reported that patients with MD-Psy were more likely to display current suicidal ideation (based on Schedule for Affective Disorders and Schizophrenia score of 3 or greater) and were over four times more likely to have a history of suicide attempts (OR=4.3, $p<0.001$), compared to patients with nonpsychotic depression. Another study found that patients with MD-Psy had double the risk of attempting suicide compared to nonpsychotic patients (OR=2.10, $p<0.05$).[5] Finally, patients with psychotic depression were more likely to display high symptom severity levels of depression and suicidal ideation post outpatient treatment (29% versus 9%, $p<0.05$) compared to nonpsychotic depressed patients.[39]

Older studies on delusional depression also reported a high risk of suicide and suicidal ideation in depressed patients with delusions.[8,18] Compared to non-delusional patients, Hamilton scores for the suicide ideation subscale were significantly higher in patients with delusional depression (1.4 ± 1.4 versus 2.8 ± 1.0).[18] Roose and associates[8] estimated that the risk of

committing suicide was over five times more likely in depressed patients with delusions compared to non-delusional patients.

An epidemiological study of over 18,000 individuals reported that 29.0% of the general population who experienced hallucinations, delusions, or both also had thoughts of suicide.[15] A four-year follow-up naturalistic study of patients with major depressive disorder with psychotic features found, at baseline, that over one-third of their study sample had been admitted to the hospital after attempting suicide.[36] Approximately 59.6% of patients with unipolar psychotic depression displayed current suicidal ideation or attempted suicide during their depressive episode. Factors that significantly attributed to severe suicidality during depressive episodes included: male gender ($p=0.049$), Hispanic ethnicity ($p=0.025$), history of suicide attempt ($p=0.006$), higher depression scores (HDRS) ($p=0.005$), and interestingly, higher Mini Mental Status Examination (MMSE) cognition scores ($p=0.027$). Conversely, older age was associated with significantly lower likelihood of a lifetime suicide attempt ($p=0.048$).[89]

While the majority of the literature has focused on suicidality, one study assessed self-harm and reported that a significantly larger proportion of patients with first-episode psychotic depression cause deliberate self-harm at first presentation ($p<0.01$) and at follow-up one year later ($p<0.05$), compared to patients with first-episode schizophrenia. The authors felt that more research on effective treatment for MD-Psy may help protect patients from acts of self-harm.[3]

III. Hospitalizations and Length of Stay

As discussed earlier, suicidality is associated with a high rate of hospitalization in patients with MD-Psy.[36] Additionally, when the worse depressive episodes were compared, patients with psychotic episodes were significantly more likely to require psychiatric inpatient admission (54.1% versus 28.6%, $p=0.0039$), compared to patients with nonpsychotic episodes of

depression.[46] Studies reported that patients with MD-Psy are two times more likely to be hospitalized for psychiatric reasons (OR=2.48, 95% CI=1.46-4.20, p<0.001), have higher rates of medical hospitalization in the last year (23.7% versus 15.0%, p=0.02), and have higher rates of lifetime psychiatric hospitalization (22.8% versus 14.7%, p=0.04), compared to patients with nonpsychotic depression.[5,14]

In one study, patients with psychotic depression endured longer lengths of hospitalization stay, compared to patients with major depression without psychosis (19.0±10.2 days versus 15.9±10.6 days, p=0.02).[56] In another study, there were no significant differences in the total number of hospitalizations (p=0.76) and total length of hospitalization stay in days (p=0.78) between patients with first-episode psychotic depression and patients with first-episode schizophrenia. Non-significance was found possibly due to the fact that psychosis was being treated in both patient groups.[3]

IV. Health Care Expenditure Costs

A review by Tyrka and associates[90] extrapolated that the costs of MD-psy treatment could be affected by treatment duration, treatment adherence, type of antidepressant utilized (newer antidepressants versus older antidepressants), use of adjunctive antipsychotic therapy (first-generation versus second-generation antipsychotics), hospitalization and associated length of stay, use of ECT, as well as short-term and long-term adverse effects of treatment. However, the economic and cost burden associated with MD-Psy has been examined in only a few studies.[3,5,14] Compared to patients with nonpsychotic major depression, patients with psychotic depression had significantly worse chronic work impairment lasting greater than one year (34.7% versus 18.3%, p=0.004).[14] Also, patients with psychotic depression exhibited worse economic functioning versus nonpsychotic depressed patients, where patients with psychotic

depression were significantly more likely to receive public assistance ($p<0.01$) and disability ($p<0.01$).[5] Crebbin and associates[3] found that the high economic burden of MD-Psy to the National Health Service (NHS) in the UK was comparable to the costs of schizophrenia in relation to adult inpatient hospitalization days, where estimated costs from 1998 to 2006 were approximately £2.6 million and £2.8 million (or approximately $5.2 million and $5.6 million US dollars in 2007), respectively.

Studies that have assessed the use of adjunctive second-generation antipsychotic therapy in patients with major depressive disorder (but also included patients with psychotic depression) reported increased costs with the use of certain antipsychotics, namely olanzapine and quetiapine.[91,92] Halpern and associates[91] found that olanzapine combination therapy was associated with significantly higher total medical costs (cost ratio [CR]=1.22; 95% CI=1.07-1.39; $p<0.01$), mental health-related medical costs (CR=1.33; 95% CI=1.11-1.59; $p<0.01$), total all-cause hospitalization (CR=1.58; 95% CI=1.30-1.92; $p<0.01$), and mental health-related hospitalization (CR=1.81; 95% CI=1.38-2.38; $p<0.01$) versus aripiprazole combination therapy. In the same study, similar results were seen with quetiapine combination therapy when compared to aripiprazole combination therapy. Nadkarni and associates[92] also found that combination therapy with olanzapine or quetiapine was associated with significantly higher total medical costs ($p<0.05$), compared to combination therapy with aripiprazole, and was primarily due to significantly higher inpatient costs ($p<0.05$).

V. Safety of Antipsychotic Agents

The safety and tolerability of both first-generation and second-generation antipsychotic agents are an obvious concern with the treatment of MD-Psy.[2,6,7,10,16,23,86,87,93] The risk of developing the major side effects of extrapyramidal symptoms (also known as extrapyramidal

syndromes or extrapyramidal side effects) such as acute dystonia (e.g., sustained contractions of the muscles of the neck, eyes, and tongue), akathisia (e.g., feelings of restlessness), parkinsonism (e.g., tremor or rigidity), tardive dystonia (e.g., late onset dystonia), and tardive dyskinesia (e.g., late onset choreiform or jerky and irregular movements) often limits the usability of first-generation antipsychotic agents. While extrapyramidal symptoms may develop in patients utilizing second-generation antipsychotic agents, the risk is much lower with these newer agents.[94,95] However, the reduced risk of extrapyramidal symptoms is accompanied by the increased risk of metabolic effects, specifically increased weight gain, hyperglycemia, and dyslipidemia.[96,97]

Studies that have assessed the treatment of psychotic depression and delusional depression with first-generation antipsychotic agents, such as perphenazine and haloperidol, reported the development of extrapyramidal symptoms in their patients.[40,66,67,75-77] Studies on MD-Psy that reported on the use of perphenazine and fluoxetine combination therapy found a 20% to 40% incidence of mild-to-moderate tremor or rigidity during treatment.[40,67] Patients on combination therapy with perphenazine and an antidepressant (sertraline or nortriptyline) had significantly more severe peak and average extrapyramidal side effect scores (both $p=0.001$) and a significantly higher incidence of tardive dyskinesia ($p=0.01$), compared to patients on antidepressants monotherapy (sertraline alone or nortriptyline alone).[77] On the contrary, Mulsant and associates[75] reported non-significant differences in akathisia and tardive dyskinesia between patients taking either perphenazine and nortriptyline combination therapy or nortriptyline monotherapy for psychotic depression. Combination therapy with perphenazine was also used in conjunction with another tricyclic antidepressant, amitriptyline, where combination therapy users experienced significantly more extrapyramidal symptoms compared to amoxapine users

($p<0.02$).[76] Interestingly, a study comparing haloperidol and amitriptyline combination treatment and risperidone monotherapy showed significantly higher parkinsonism subscale scores with risperidone ($p=0.028$), a second-generation antipsychotic agent, with no significant differences in the dystonia and dyskinesia subscale scores ($p=0.82$ and $p=0.16$, respectively).[66]

Although there is a reduced risk of developing extrapyramidal symptoms with second-generation antipsychotic agents,[95] questions remain regarding the safety of these agents in the treatment of MD-Psy.[23] Four studies utilizing second-generation antipsychotic agents reported the development of extrapyramidal symptoms.[71-73,98] Specifically, reports of tremor or rigidity occurred in trials where patients were taking quetiapine, olanzapine, or amisulpride,[9,71,73,98] and akathisia developed in 63% of patients taking combination therapy with aripiprazole and escitalopram.[72] Akathisia and tardive dyskinesia developed in patients taking olanzapine, but no differences were seen between combination therapy and monotherapy groups.[49] On the other hand, clozapine, a second-generation antipsychotic used primarily as a last resort for refractory patients, may reduce or mitigate antipsychotic-induced tardive dyskinesia. However, the severe risk of agranulocytosis with clozapine therapy must be weighed against its benefits.[84,95]

The metabolic risks associated with second-generation antipsychotic agents have been addressed by several studies.[9,49,68-71] The STOP-PD study, a double-blind randomized controlled trial, assessed the metabolic safety and tolerability of combination therapy and monotherapy with olanzapine (a second-generation antipsychotic agent).[49,50] Patients with psychotic depression were randomized to receive combination therapy (olanzapine and sertraline) or antipsychotic monotherapy (olanzapine alone), where significant increases in weight gain, hyperglycemia, triglycerides, and cholesterol were observed during the course of the 12-week trial ($p<0.001$, $p=0.006$, $p<0.001$, and $p<0.001$, respectively).[49] Weight gain (mean increase of 3.3±6.6 pounds)

and increase in appetite were common side effects in a six-week long open-label study utilizing olanzapine and fluoxetine combination therapy for the treatment of MD-Psy.[69] A study of two pooled randomized trials of 249 utilizers of placebo, olanzapine monotherapy, and olanzapine and fluoxetine combination therapy showed a significant weight gain in olanzapine monotherapy compared to placebo therapy ($p=0.01$). Conversely, no significant differences between combination therapy versus placebo ($p=0.447$) and combination therapy versus olanzapine monotherapy were observed ($p=0.174$).[68] Quetiapine use in MD-Psy is also associated with mean changes in weight gain.[71] Wijkstra and associates[9] conducted a randomized, double-blind study and assessed the safety of antidepressant monotherapy (imipramine or venlafaxine) and combination therapy and found that combination treatment with quetiapine and venlafaxine led to significantly more weight gain compared to monotherapy ($p<0.01$). And an open-label follow-up study with the same treatment showed a significantly higher mean increase in weight with combination therapy, compared to monotherapy during the continuation treatment period ($p=0.002$).[74]

SIGNIFICANCE AND PURPOSE OF STUDY

MD-Psy is a documented public health problem associated with considerable morbidity and mortality.[4,6] Epidemiological studies report that 14.7% to 25.3% of patients diagnosed with major depression have psychotic features, and this proportion is estimated to be much higher in the geriatric population with major depressive disorder at 44.7%.[5,12,13] Compared to patients with nonpsychotic depression, patients with MD-Psy experience more severe depression, higher psychosocial impairment, worse psychomotor agitation, more indecisiveness, and higher frequencies of insomnia.[5,14,35] They are also more likely to have worse health outcomes related to longer persisting depression, as well as increased risk of relapse, hospitalizations, suicide, and

financial dependency.[5] The financial burden of MD-Psy is apparent, where inpatient hospitalization costs to society nearly equate the costs associated with schizophrenia.[3] While this disorder is associated with high rates of relapse and suffering, the treatment of MD-Psy has not been sufficiently studied.[9] Therefore, additional MD-Psy studies examining effective and safe medication treatments, medication adherence and persistence, suicide attempts, health care utilization (e.g., hospitalizations and lengths of stay), and health care costs are warranted.

Currently, there is no clear consensus regarding the treatment strategy for MD-Psy.[2] Treatment guidelines and algorithms for psychotic depression support the use of ECT or combination therapy with an antipsychotic agent and antidepressant as first-line therapy;[7,10,11] however, there is considerable debate about which pharmacological treatment is best.[2,99] More evidence on the efficacy and safety of second-generation antipsychotic agents in MD-Psy is needed.[2] While the risk of developing extrapyramidal symptoms is reduced with these newer agents, the metabolic adverse effects associated with long-term continuation and maintenance treatment in MD-Psy must be further addressed.[2,95]

There is not a strong consensus on how long patients should be maintained on their medications.[2] Only one study has assessed medication adherence (estimated as medication usage as a percentage of time).[80] There is a dearth of studies concerning medication adherence in MD-Psy. Validated adherence measures such as medication possession ratio (MPR), proportion of days covered (PDC), and medication persistence may help shed more light on the appropriateness of therapy and long-term continuation.[100-102]

The high risk of hospitalization in MD-Psy has been established in previous studies comparing patients with psychotic depression to nonpsychotic depressed patients.[5,14,46] One study compared the hospitalization rates of patients with first-episode psychotic depression to

that of first-episode schizophrenia.[3] Two studies published in 2013 found that total hospitalization, mental health-related hospitalization, and emergency room visits were significantly higher in patients on combination treatment with olanzapine plus an antidepressant or quetiapine plus an antidepressant, compared to combination treatment with aripiprazole and an antidepressant ($p<0.05$); however, these studies were not specific to depressed patients diagnosed with just MD-Psy.[91,92] There remains a lack of studies assessing whether differences in medication therapy (e.g., monotherapy versus combination therapy) play a role in decreasing the hospitalization rates and associated lengths of stay.

The financial burden of MD-Psy to society has been explored by only a few studies.[3,5,14] One study has assessed the inpatient costs of patients with MD-Psy by comparing it to the inpatient costs associated with schizophrenia.[3] While worse economic functioning and chronic work impairment have been established, there is an absence of studies providing actual cost estimates related to MD-Psy.[5,14] Although two studies reported significantly lower total medical costs, mental health-related costs, inpatient costs, and outpatient costs with the use of combination treatment with aripiprazole over combination treatment with olanzapine or quetiapine ($p<0.05$), the studies included patients with other depression diagnoses, not just MD-Psy.[91,92] More cost studies are needed to assess the expenditures associated with prescription utilization, inpatient and outpatient visits, and suicides in order to better comprehend the seriousness of MD-Psy.

The primary purpose of the proposed study is to assess medication therapy for patients with unipolar MD-Psy in relation to medication adherence and persistence, reduced suicide attempts, health care utilization, health care costs, and incidence of medication-related adverse events using real-world data. Specifically, two medication therapy cohorts will be compared: an

antidepressant monotherapy cohort (AD cohort) and an antidepressant and second-generation antipsychotic combination cohort (AD/SGA cohort). The proposed study also aims to provide enhanced understanding of this severe subtype of major depressive disorder and to provide information to fill the gaps in knowledge that clinicians and decision-makers may use when considering treatment options for unipolar MD-Psy. To our knowledge, this study is the first known retrospective analysis utilizing a large database claims dataset to primarily assess unipolar MD-Psy.

STUDY OBJECTIVES

Specifically, the objectives of the present study were to:

- **Objective 1:** To describe and compare the baseline socio-demographic and clinical characteristics of Texas Medicaid patients with MD-Psy who utilize either antidepressant monotherapy (AD cohort) or combination therapy with an antidepressant and a second-generation antipsychotic (AD/SGA cohort).
- **Objective 2:** To describe and compare the post-index clinical characteristics of the AD and AD/SGA cohorts.
- **Objective 3:** To determine if medication adherence rates (medication possession ratio – MPR and proportion of days covered – PDC) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.
- **Objective 4:** To determine if the risk of medication nonpersistence differs between patients in the AD and AD/SGA cohorts, while controlling for covariates.
- **Objective 5:** To determine if rates of post-index suicide ideation and suicide attempts differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.
- **Objective 6:** To identify if post-index health care utilization rates (psychotic depression-related hospitalizations, length of psychotic depression-related hospitalization stay, psychotic depression-related outpatient/emergency department visits, all-cause hospitalizations, length of all-cause hospitalization stay, all-cause outpatient/emergency department visits) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.
- **Objective 7:** To determine if post-index adjusted health care costs (psychotic depression-related medication, psychotic depression-related medical, psychotic depression-related

total, all-cause medication, all-cause medical, and all-cause total costs) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.

- **Objective 8:** To determine if the risks of medication therapy (incident dyslipidemia, incident diabetes mellitus, and incident extrapyramidal symptoms) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.

STUDY HYPOTHESES

The following hypotheses were tested:

- No hypotheses were generated for Objectives 1 and 2.
- **H_{03A}:** The likelihood of being adherent as measured by MPR $\geq$ 80% to antidepressant therapy does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{03B}:** The likelihood of being adherent as measured by PDC $\geq$ 80% to antidepressant therapy does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{04A}:** The time, in days, to antidepressant medication nonpersistence (using a 45-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{04B}:** The time, in days, to antidepressant medication nonpersistence (using a 30-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.

- **H_{04C}:** The time, in days, to antidepressant medication nonpersistence (using a 60-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{05A}:** The likelihood of having post-index suicide ideation does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{05B}:** The likelihood of having a post-index suicide attempt does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{06A}:** The number of post-index psychotic depression-related hospitalizations does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{06B}:** The number of post-index psychotic depression-related hospitalization days (sum of hospital stays, in days) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{06C}:** The number of post-index psychotic depression-related outpatient/emergency department visits does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{06D}:** The number of post-index all-cause hospitalizations does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{06E}:** The number of post-index all-cause hospitalization days (sum of hospital stays, in days) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{06F}:** The number of post-index all-cause outpatient/emergency department visits does not differ between the AD and AD/SGA cohorts, while controlling for covariates.

- **H_{07A}:** The post-index psychotic depression-related medication costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{07B}:** The post-index psychotic depression-related medical costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{07C}:** The post-index psychotic depression-related total costs (psychotic depression-related prescription and psychotic depression-related medical costs) do not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{07D}:** The post-index all-cause medication costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{07E}:** The post-index all-cause medical costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{07F}:** The post-index all-cause total costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{08A}:** The progression to the first diagnosis of dyslipidemia (after a 45-day post-index period) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{08B}:** The progression to the first diagnosis of diabetes mellitus (after a 45-day post-index period) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.
- **H_{08C}:** The progression to the first diagnosis of extrapyramidal symptoms post-index does not differ between the AD and AD/SGA cohorts, while controlling for covariates.

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Chapter 2: Methodology

CHAPTER OVERVIEW

This chapter describes the methodology that was utilized to test the present study's objectives and hypotheses. Detail is provided for the following: data source, inclusion and exclusion criteria, data extraction, study timeframe, study design, and independent and dependent variables. Specific statistical analyses, test assumptions, and sample size calculations are also presented.

INSTITUTIONAL REVIEW BOARD APPROVAL

The University of Texas at Austin Institutional Review Board (IRB) deemed that IRB review and oversight was not necessary or required for the present study as it did not involve human subject research as defined by Common Rule (45 CFR 46) or Food and Drug Administration Regulations (21 CFR 50 & 56). An official letter of Non Human Subject Research Determination (FWA# 00002030) was granted by the Office of Research Support at The University of Texas at Austin in lieu of IRB approval.

DATA

I. Data Source: Texas Medicaid

The proposed study utilized prescription, medical, and eligibility data from The Texas Department of Health Medicaid Program Database. The Texas Medicaid Program is a federal and state cooperative venture that provides medical and prescription coverage for needy persons, such as low-income families, pregnant women, children, caretakers of children, and those with disabilities. At the state level, the program is administered by the Health and Human Services

Commission (HHSC), and at the federal level, Medicaid is overseen by the Centers for Medicare & Medicaid Services (CMS). Federal laws set minimum standards, while the state determines individual program criteria. The Texas Medicaid Program covers program-approved treatment for acute health care, such as inpatient, outpatient, prescription, and physician services. During the 2011 federal fiscal year, Medicaid expenditures represented 26.0 percent of the state's total expenditures, and in December of 2011, approximately 3.7 million Texans (or 14.3 percent of the total state population) depended on the Texas Medicaid Program for health insurance services or long-term care support.[1]

II. Inclusion Criteria

Patients with a diagnosis of "severe major depressive disorder with psychotic features" identified using *International Classification of Diseases, Ninth Revision, Clinical Modifications* (ICD-9-CM) diagnosis codes 296.24 and 296.34 between September 1, 2007 and December 31, 2012 were selected. The following inclusion criteria was met: 1) aged 18 to 63 years; 2) have at least two prescription claims with different dates within the period of March 1, 2008 to December 31, 2012 for an antidepressant listed in Table 2.1 (antidepressant cohort or AD cohort) – or – have at least two claims for an antidepressant listed in Table 2.1 and have at least two claims for an oral or injectable second-generation antipsychotic agent, such as asenapine, aripiprazole, iloperidone, lurasidone, olanzapine, olanzapine and fluoxetine, paliperidone, risperidone, quetiapine, or ziprasidone (antidepressant and second-generation antipsychotic combination cohort or AD/SGA cohort); 3) have at least six months of continuous Medicaid coverage prior to their index date; and 4) have at least 12 months of continuous Medicaid coverage after their index date.

Table 2.1: Antidepressant Medications

Medication Class	Medication
Selective serotonin reuptake inhibitor	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
Selective serotonin reuptake inhibitor and partial agonist	Vilazodone
Serotonin-norepinephrine reuptake inhibitor	Desvenlafaxine, Duloxetine, Levomilnacipran, Venlafaxine
Aminoketone	Budeprion, Buproprion
Triazolopyridine	Nefazodone, Trazodone
Tetracycline	Maprotiline, Mirtazapine
Tricyclic antidepressant	Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepine, Imipramine, Nortriptyline, Protriptyline, Trimipramine
Monoamine oxidase inhibitor	Phenelzine, Selegiline, Tranylcypromine

III. Exclusion Criteria

In order to better control for confounding associated with other disorders and disease states, patients were excluded if they had an ICD-9-CM diagnosis of dementia (290.xx); schizophrenia (295.xx); pervasive development disorder (299.xx); mental retardation (317.xx-319.xx); other cerebral degenerations (331.xx); Parkinson's disease (332.xx); senility without mention of psychosis (797.xx); or manic depression, bipolar disorder, or cyclothymic disorder (296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.80, 296.81, 296.89, 301.13).[2,3] Patients were also excluded if they had a claim at any time during the pre-index or post-index periods for the following: electroconvulsive therapy (based on ICD-9-CM codes 94.26 and 94.27 or current procedural terminology codes 90870 and 90871), clozapine medication, or a first-generation antipsychotic agent.[4-6]

IV. Index Date

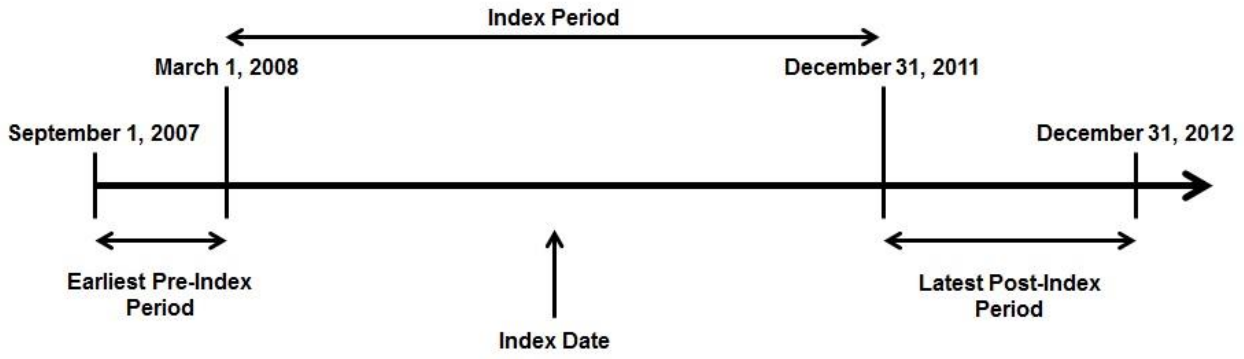
For both cohorts, the index date was defined as the first prescription claim date for an antidepressant medication listed in Table 2.1. Patients in the AD cohort had at least two post-index prescription claims for an antidepressant on different dates with no antidepressant prescription claims six months prior to the index date. These patients did not have a second-generation antipsychotic prescription claim six months prior to and twelve months after the index date. For the AD/SGA cohort, patients had at least two post-index prescription claims for an antidepressant as well as at least two prescription claims for a second-generation antipsychotic agent. The first prescription claim for a second-generation antipsychotic had to occur on the same day as the first antidepressant claim (also known as the index date), where at least a 30-day overlap period between the antidepressant and second-generation antipsychotic was required to

ensure combined therapy utilization.[4] Similarly, patients in the AD/SGA cohort did not have any prescription claims for a second-generation antipsychotic six months prior to the index date.

V. Data Extraction and Timeframe

Texas Medicaid prescription claims and inpatient, outpatient, and physician visit claims from September 1, 2007 to December 31, 2012 were extracted for patients who had a diagnosis and received medication for MD-Psy. The index identification period ranged from March 1, 2008 to December 31, 2011 to allow for the minimum 18-month study period of 6 months of continuous Medicaid coverage prior to the index date and 12 months of follow-up claims after the index date (Figure 2.1). For example, if the index date (i.e., the first antidepressant claim date) for Patient X is March 1, 2008 then Patient X's index period would end on February 28, 2009 to allow for one year of follow-up data. If Patient Y's index date is December 1, 2010, then Patient Y's index period would end one year later on November 30, 2011. However, patients with index dates that fall either before March 1, 2008 or after December 31, 2011 were excluded from the study due to the lack of patient claims data (i.e., six months of pre-index data and 12 months of post-index data).

Figure 2.1: Data Extraction and Subject Identification Period



STUDY DESIGN

The present study employed a retrospective cohort design. Patients with MD-Psy were classified into two different cohorts: antidepressant medications only (AD cohort) versus antidepressant and SGA combination therapy (AD/SGA cohort). Comparisons between these two cohorts were made in relation to antidepressant adherence, antidepressant persistence, suicide ideation and attempts, health care utilization (i.e., psychotic depression-related and all-cause hospitalizations, hospitalization lengths of stay, and outpatient/emergency department visits), health care costs (i.e., psychotic depression-related and all-cause medication, medical, and total costs), and medication-related adverse outcomes (i.e., development of dyslipidemia, diabetes mellitus, or extrapyramidal symptoms).

STUDY VARIABLES

I. Dependent Variables

The dependent variables for the proposed study included the following: 1) medication possession ratio, 2) proportion of days covered, 3) medication persistence, 4) suicide ideation, 5) suicide attempts, 6) psychotic depression-related hospitalizations, 7) length of psychotic depression-related hospitalization stay, 8) psychotic depression-related outpatient/emergency department visits, 9) all-cause hospitalizations, 10) length of all-cause hospitalization stay, 11) all-cause outpatient/emergency department visits, 12) psychotic depression-related medication costs, 13) psychotic depression-related medical costs, 14) psychotic depression-related total costs, 15) all-cause medication costs, 16) all-cause medical costs, 17) all-cause total costs, 18) incidence of dyslipidemia, 19) incidence of diabetes mellitus, and 20) incidence of extrapyramidal symptoms.

Medication Possession Ratio and Proportion of Days Covered

Medication adherence, also known as medication compliance, is defined by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen."[7] Adherence can be measured directly in prospective studies, for example, through the use of direct observation, or it can be measured indirectly with retrospective database claims analyses when direct methods are not available.[7,8] Although there are several indirect measures of medication adherence, a study by Karve and associates[9] recommended using the medication possession ratio (MPR) and proportion of days covered (PDC) measures when working with administrative database claims data.

There are advantages and disadvantages to utilizing MPR and PDC measures of medication adherence. For example, an advantage to using MPR is that it is commonly recognized and highly utilized in administrative database analyses. However, a disadvantage of MPR is that it may be less accurate (i.e., overestimates adherence) in instances when duplicative therapy or medication switching occur. While PDC is advantageous in providing more conservative estimates of adherence with switching and duplication, it cannot be used to assess excessive medication use (values fall between 0 and 1) and is more complicated to compute than MPR.[8] Since MPR and PDC have their advantages and limitations, both were utilized as proxies to medication adherence.

MPR is operationalized as the total days' supply of medication divided by the total days in a given period.[8,10] MPR was categorized into two groups – MPRs less than 80% (not adherent) and MPRs greater than or equal to 80% (adherent).[10,11] MPR values greater than 1.0 were truncated to 1.0.[8] For the AD cohort, MPR represented adherence to any antidepressant therapy. For the AD/SGA cohort, MPR also represented adherence to antidepressants only since there is no standard length of second-generation antipsychotic therapy used to treat MD-Psy. MPR was measured using prescription claims data and physician visit claims data since injectable second-generation antipsychotics were provided during physician office visits (Table 2.2).

MPR = (total days' supply of medication * 100%) / 365 days of follow-up

PDC is operationalized as the proportion of days in which medication is available over the total number of days in a given period.[8,10] PDC was also categorized into two groups using the same cut-off point of 80% to determine adherence and non-adherence.[11] Like MPR above, PDC was calculated to measure adherence to any antidepressant therapy for both cohorts. PDC was measured using prescription and physician visit claims data (Table 2.2).

PDC = (total days of available medication * 100%) / 365 days of follow-up

Table 2.2: Outpatient and Physician Visit Claims for Injectable Antipsychotics

Injectable Antipsychotic	J Code(s)	Day Supply Estimate
Aripiprazole	J0400	Monthly (no sooner than every 26 days)[a,b]
Olanzapine	J2358	14 days or 28 days (dose-dependent)[c]
Paliperidone	J2426	Monthly[b,d]
Risperidone	J2794	14 days[e]
Ziprasidone	J3486	Acute dosing (every 2 to 4 hours)[f]

[a]Abilify Maintena (aripiprazole) extended-release intramuscular injection package insert. [b]Monthly as estimated as a 30 days supply. [c]Zyprexa Relprevv (olanzapine injectable suspension) package insert. Due to the lack of dosing information in claims dataset, day supply was estimated as 28 days. [d]Invega Sustenna (paliperidone palmitate injectable suspension) package insert. [e]Risperdal Consta (risperidone long-acting injection) package insert. [f]Geodon® (ziprasidone) package insert. Acute dosing was estimated as 1 day supply.

Medication Persistence

Persistence, also known in the literature as persistency or continuous adherence, is defined by the ISPOR Medication Compliance and Persistence Work Group as "the duration of time from initiation to discontinuation of therapy."[7] Persistence allows for the incorporation of time when analyzing adherence and represents the amount of time until medication discontinuation occurs. Medication discontinuation, or nonpersistence, is indicated by reaching a "permissible gap," where gaps of 30 or 60 days are often utilized.[10]

In the present study, the unit of time was measured in days, and a 45-day permissible gap was utilized. Secondary analyses using 30-day and 60-day gaps were also assessed. The cohorts were compared on the persistence of any antidepressant use. For the AD/SGA cohort, persistence on any second-generation antipsychotic was measured separately to determine the average time MD-Psy patients utilized second-generation antipsychotic therapy. Like MPR and PDC, medication persistence was measured using prescription and physician visit claims data.

Suicide Ideation

Using inpatient, outpatient, and physician visit claims data post-index, suicide ideation was identified using ICD-9-CM code V62.84. In addition, a variable was created that indicated whether a patient had either (1) no suicide ideation diagnosis or (2) at least one suicide ideation diagnosis during the follow-up period.

Suicide Attempts

Using inpatient, outpatient, and physician visit claims data post-index, suicide attempts were identified using ICD-9-CM codes E950.x-E959.x.[3] In addition, a variable was created that indicated whether a patient had either (1) no suicide attempt diagnosis or (2) at least one suicide attempt diagnosis during the follow-up period.

Psychotic Depression-Related Hospitalizations

Psychotic depression-related hospitalizations were identified using ICD-9-CM codes 296.24 and 296.34 for MD-Psy. The number of hospitalizations was identified using data from inpatient hospital claims post-index.

Length of Psychotic Depression-Related Hospitalization Stay

Once a psychotic depression-related hospitalization was identified post-index, the associated length of hospitalization stay (in days) was calculated for each psychotic depression-related hospitalization. All lengths of stay were summated to represent the total psychotic depression-related hospital days for each patient.

Length of Hospitalization Stay = (Final Stay Date – Initial Stay Date) + 1.

Psychotic Depression-Related Outpatient/Emergency Department Visits

Psychotic depression-related outpatient/emergency department visits were identified using ICD-9-CM codes 296.24 and 296.34 for MD-Psy. The number of these outpatient and emergency department visits was counted using outpatient claims data post-index.

Outpatient and emergency department visits were aggregated into one variable due to the small sample size of emergency department visits in the dataset. Although the aggregation of hospitalizations and emergency department visits was considered, this was deemed a less appropriate option since (1) emergency department visits did not necessarily lead to hospitalizations (especially if patients used them similarly to an outpatient visit) and (2) it would not allow for strict comparisons to the previous literature regarding hospitalizations and lengths of stay.

All-Cause Hospitalizations

The number of all-cause hospitalizations was identified using data from inpatient hospital claims post-index.

Length of All-Cause Hospitalization Stay

Once all hospitalizations were identified post-index, the associated lengths of hospitalization stay (in days) for each hospitalization was calculated. All lengths of stay were summated to represent the total hospital days for each patient.

Length of Hospitalization Stay = (Final Stay Date – Initial Stay Date) + 1.

All-Cause Outpatient/Emergency Department Visits

The number of all-cause outpatient/emergency department visits was identified using outpatient claims data post-index.

Psychotic Depression-Related Medication Costs

Psychotic depression-related medication costs included all post-index direct prescription costs to Texas Medicaid for AD or AD/SGA combination therapy. Costs were adjusted to 2012 US dollars and summated. Injectable medication costs associated with physician and outpatient visits were also included based on J code-associated costs (Table 2.3).

Table 2.3: J Codes Associated with Injectable Antipsychotic Medications

First-Generation Antipsychotic Injectable	J Code
Chlorpromazine	J3230
Fluphenazine	J2680
Haloperidol	J1630, J1631
Perphenazine	J3310
Second-Generation Antipsychotic Injectable	**J Code**
Aripiprazole	J0400
Olanzapine	J2358
Paliperidone	J2426
Risperidone	J2794
Ziprasidone	J3486

Psychotic Depression-Related Medical Costs

Psychotic depression-related medical costs included all post-index direct medical costs to Texas Medicaid for inpatient, outpatient, and physician visits based on ICD-9-CM codes 296.24 and 296.34 for MD-Psy. Costs were adjusted to 2012 US dollars and summated.

Psychotic Depression-Related Total Costs

Psychotic depression-related total costs included all post-index direct psychotic depression-related medication and medical costs to Texas Medicaid. Costs were adjusted to 2012 US dollars and summated.

All-Cause Medication Costs

All-cause medication costs included all post-index direct prescription costs to Texas Medicaid. Costs were adjusted to 2012 US dollars and summated.

All-Cause Medical Costs

All-cause medical costs included all post-index direct medical costs to Texas Medicaid for inpatient, outpatient, and physician visits. Costs were adjusted to 2012 US dollars and summated.

All-Cause Total Costs

All-cause total costs included all post-index direct prescription and medical costs to Texas Medicaid. Costs were adjusted to 2012 US dollars and summated.

Cumulative Incidence of Dyslipidemia

The cumulative incidence of dyslipidemia was operationalized as a simple ratio of the number of new cases of dyslipidemia that occurred during the 1-yr follow-up period divided by the total number of susceptible cases without dyslipidemia at 45 days after the index date. Patients considered susceptible to dyslipidemia had no diagnosis of dyslipidemia during the six-month pre-index period plus 45 days post-index. New onset dyslipidemia was measured as 1) the utilization of one or more dyslipidemia medications based on drug names[12] and AHFS codes (24.06.04, 24.06.05, 24.06.05, 24.06.06, 24.06.08, 24.06.92),[13,14] or 2) as one or more diagnoses of dyslipidemia (based on ICD-9-CM codes 272.xx).[15,16] Also, a Cox proportional hazards ratio was calculated between cohorts based on the time, in days, from 45 days after the index date to the first diagnosis of dyslipidemia.

Cumulative Incidence of Diabetes Mellitus

The cumulative incidence of diabetes mellitus was operationalized as a simple ratio of the number of new diagnoses of diabetes mellitus that occurred during the 1-yr follow-up period divided by the total number of susceptible cases not diagnosed with diabetes mellitus at 45 days

after the index date. Patients considered susceptible to diabetes mellitus had no diagnosis of diabetes mellitus (types I or II) during the six-month pre-index period plus 45 days post-index. New onset diabetes mellitus was measured as: 1) the utilization of one or more anti-diabetic medications based on drug name[12] or by AHFS codes (68.20.02, 68.20.03, 68.20.04, 68.20.05, 68.20.06, 68.20.08, 68.20.16, 68.20.18, 68.20.20, 68.20.28, 68.20.92),[13,14] or 2) one or more diagnoses of diabetes mellitus (based on ICD-9-CM codes 250.xx, diabetes mellitus; 357.2, diabetic nephropathy; 362.01-362.02, diabetic retinopathy; and 366.41, diabetic cataract).[16,17] Also, a Cox proportional hazards ratio was calculated between cohorts based on the time, in days, from 45 days after the index date to the first diagnosis of diabetes mellitus.

Cumulative Incidence of Extrapyramidal Symptoms

The cumulative incidence of extrapyramidal symptoms was operationalized as a simple ratio of the number of new diagnoses of extrapyramidal symptoms that occurred during the 1-yr follow-up period divided by the total number of susceptible cases not diagnosed with extrapyramidal symptoms at the index date. Patients considered susceptible to extrapyramidal symptoms had no diagnosis of extrapyramidal symptoms during the six-month pre-index period. Since the onset of extrapyramidal symptoms may occur as early as a few hours to days post exposure to three months to a year later,[18,19] new onset extrapyramidal symptoms were measured as one or more diagnoses of extrapyramidal symptoms based on ICD-9-CM codes (333.1, 333.2, 333.3, 333.72, 333.85, 333.90, 333.92, 333.99, 781.0, and 332.1) that occurred at any time after the index date. Also, a Cox proportional hazards ratio was calculated between cohorts based on the time, in days, from the index date to the first diagnosis of an extrapyramidal symptom.

Table 2.4 provides a listing of the dependent variables for the present study.

Table 2.4: Operational Definition of Dependent Variables

Variable	Operational Definition
Medication Possession Ratio	Dichotomous MPR 0=Not adherent (MPR < 80%) 1=Adherent (MPR ≥ 80%)
Proportion of Days Covered	Dichotomous PDC 0=Not adherent (PDC < 80%) 1=Adherent (PDC ≥ 80%)
Medication Persistence	Continuous Number of days before a permissible gap
Suicide Ideation	Dichotomous 0=No suicide ideation diagnosis 1=One or more suicide ideation diagnoses
Suicide Attempts	Dichotomous 0=No suicide attempt diagnosis 1=One or more suicide attempt diagnoses
Psychotic Depression-Related Hospitalizations	Count Number of post-index hospitalizations with ICD-9-CM codes 296.24 and 296.34
Length of Psychotic Depression-Related Hospitalization Stay	Count Number of post-index hospitalization days associated with psychotic depression-related hospitalizations
Psychotic Depression-Related Outpatient/ Emergency Department Visits	Count Number of post-index outpatient/emergency department visits with ICD-9-CM codes 296.24 and 296.34
All-Cause Hospitalizations	Count Number of all-cause hospitalizations post-index
Length of All-Cause Hospitalization Stay	Count Number of all-cause hospitalization days post-index
All-Cause Outpatient/ Emergency Department Visits	Count Number of all-cause outpatient/emergency department visits post-index
Psychotic Depression-Related Medication Costs	Continuous Summated, post-index direct costs to Texas Medicaid for antidepressant, antipsychotic, and other psychotic depression-related prescriptions adjusted to 2012 US dollars
Psychotic Depression-Related Medical Costs	Continuous Summated, post-index direct costs to Texas Medicaid for inpatient, outpatient, and physician visits with ICD-9-CM codes 296.24 and 296.34 adjusted to 2012 US dollars
Psychotic Depression-Related Total Costs	Continuous Summated, post-index psychotic depression-related medication and medical costs to Texas Medicaid adjusted to 2012 US dollars

Table 2.4: Operational Definition of Dependent Variables (continued)

Variable	Operational Definition
All-Cause Medication Costs	Continuous Summated, post-index direct costs to Texas Medicaid for all prescriptions adjusted to 2012 US dollars
All-Cause Medical Costs	Continuous Summated, post-index direct costs to Texas Medicaid for inpatient, outpatient, and physician visits adjusted to 2012 US dollars
All-Cause Total Costs	Continuous All post-index direct costs to Texas Medicaid adjusted to 2012 US dollars and summated
Cumulative Incidence of Dyslipidemia	Continuous Cumulative Incidence: total new cases of dyslipidemia divided by total susceptible at index date based on ICD-9-CM codes (272.xx) and AHFS codes (24.06.04, 24.06.05, 24.06.05, 24.06.06, 24.06.08, 24.06.92) Continuous Survival time, in days, until onset of dyslipidemia
Cumulative Incidence of Diabetes Mellitus	Continuous Cumulative Incidence: total new cases of diabetes mellitus divided by total susceptible at index date based on ICD-9-CM codes (250.xx) and AHFS codes (68.20.02, 68.20.03, 68.20.04, 68.20.05, 68.20.06, 68.20.08, 68.20.16, 68.20.18, 68.20.20, 68.20.28, 68.20.92) Continuous Survival time, in days, until onset of diabetes mellitus
Cumulative Incidence of Extrapyramidal Symptoms	Continuous Cumulative Incidence: total new cases of extrapyramidal symptoms divided by total susceptible at index date ICD-9-CM codes 333.1, 333.2, 333.3, 333.72, 333.85, 333.90, 333.92, 333.99, 781.0, and 332.1 Continuous Survival time, in days, until onset of extrapyramidal symptoms

II. Independent Variables

The primary independent variable was the patient cohort (AD cohort versus AD/SGA cohort). Demographic and clinical variables included: age, race/ethnicity, gender, urban residence, Charlson Comorbidity Index (CCI) score, tobacco use and/or dependence, and antidepressant persistence using a 45-day permissible gap (for Objectives 5 through 8 only). Table 2.5 provides a listing of the independent variables.

Table 2.5: Operational Definition of Independent Variables

Primary Independent Variable	**Operational Definition**
Patient Cohort	Dichotomous 0=AD cohort 1=AD/SGA cohort
Baseline Socio-Demographic Variable	**Operational Definition**
Age	Continuous Age at index (in years)
Race/Ethnicity	Categorical 1=Caucasian 2=African American 3=Hispanic 4=Other (Asian or Unknown)
Gender	Dichotomous 0=Male 1=Female
Urban Residence	Dichotomous 0=No (rural residence) 1=Yes (urban residence)
Baseline Clinical Variable	**Operational Definition**
CCI	Continuous Weight index based on Dartmouth-Manitoba adaptation of CCI
Post-Index Clinical Variable	**Operational Definition**
Tobacco Use and/or Dependence	Dichotomous 0=No (no post-index claim) 1=Yes (at least one post-index claim)
Antidepressant Persistence	Continuous Persistence on antidepressants using a 45-day gap

Patient Cohort

The patient cohort variable was dichotomized as the AD cohort and the AD/SGA cohort. The AD cohort comprised patients who used antidepressant therapy only, and the AD/SGA cohort represented patients who utilized both antidepressant and second-generation antipsychotic therapy.

Age

Patient age, measured in years and truncated to two digits without decimals, was defined based on the age at the index date.

Gender

Gender was dichotomized as male or female.

Race/Ethnicity

Race/ethnicity was categorized into four groups: Caucasians, African Americans, Hispanics, and Other. Other included Asians and patients with Unknown race/ethnicity.

Urban Residence

Urban residence variables were dichotomized as either "no" (i.e., rural residence) or "yes" (i.e., urban residence). Urban and rural residences were identified by Texas Medicaid based on Medicaid Rural Service areas.

Charlson Comorbidity Index (CCI)

Comorbidities, also known as comorbid diseases or illnesses, play an important prognostic role in determining mortality. In 1987, Charlson and associates[20] developed the Charlson Comorbidity Index (CCI) in order to predict the risk of one-year mortality due to

comorbidities. The CCI is a weighted index that incorporates both the quantity (number) and quality (seriousness is ranked as 1, 2, 3, or 6) of comorbid disease, where patients with higher summated scores are considered to have higher risks of comorbid death.[20] Adaptations of the CCI (Deyo,[21] Dartmouth-Manitoba,[22] D'Hoore[23]) have been utilized in retrospective database analysis studies that assessed comorbidity data through ICD-9-CM codes.[21-25] While the Deyo and Dartmouth-Manitoba are the most utilized adaptations, the Dartmouth-Manitoba method is considered to utilize a less strict interpretation of the CCI definitions.[22,25] Therefore, the Dartmouth-Manitoba adaptation was utilized to determine the baseline comorbidity score (Table 2.6).

Table 2.6: Charlson Comorbidity Index (CCI) and Dartmouth-Manitoba Adaptation

CCI Comorbid Condition	CCI Weight	Dartmouth-Manitoba ICD-9-CM codes
Myocardial infarction	1	410.xx, 412*
Congestive heart failure	1	402.01, 402.11, 402.91, 425.x, 428.x, 429.3, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93
Peripheral vascular disease	1	440.x*, 441.x*, 442.x*, 443.1-443.9*, 447.1*, 785.4*, 38.13-38.14(P)*, 38.16(P)*, 38.18(P)*, 38.33-38.34(P)*, 38.36(P)* 38.38(P)*, 38.43-38.44(P)*, 38.46(P)*, 38.48(P)*, 39.22-39.26(P)*
Cerebrovascular disease	1	362.34, 430-436, 437-437.1, 437.9, 438, 781.4, 784.3, 997.0, 38.12(P), 38.42(P)
Dementia	1	290.x*, 331-331.2*
Chronic pulmonary disease	1	415.0*, 416.8-416.9*, 491.x-494*, 496*
Connective tissue disease	1	710.x, 714.x
Ulcer disease	1	531.xx-534.xx
Mild liver disease	1	571.2*, 571.5-571.6*, 571.8-571.9*
Diabetes	1	250.0x-250.3x*
Diabetes with end organ damage	2	250.4x-250.9x*†
Hemiplegia	2	342.x, 344.x
Moderate or severe renal disease	2	585-586*, V42.0*, V45.1*, V56.x*, 39.27(P)*, 39.42(P)*, 39.93-39.95(P)*, 54.98(P)*
Any tumor	2	140.x-171.x*, 174.x-195.x*, 200.xx-208.x*, 273.0*, 273.3*, V10.46*, 60.5(P)*, 62.4-62.41(P)
Leukemia	2	
Lymphoma	2	
Moderate or severe liver disease	3	572.2-572.4*, 456.0-456.2x*, 39.1(P)*, 42.91(P)*†
Metastatic solid tumor	6	196.x-199.x*†
AIDS	6	042.x-044.x

(P) follows all ICD-9-CM codes that describe procedures rather than diagnoses (Vol.III).
*The codes with asterisks are included in the definition of a comorbidity if they are listed during either index or prior hospital discharges; other codes are included only if recorded prior to the index discharge. Each asterisk applies to all codes within the indicated range.
†In the Dartmouth-Manitoba algorithm, these comorbidities take precedence over less severe comorbidities involving the same organ system.
Adapted from: Needham DM, Scales DC, Laupacis A, Pronovost PJ. A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. J Crit Care. 2005; 20(1):12-19. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol. 1993; 46(10):1075-1079; discussion 1081-1090. D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. J Clin Epidemiol. 1996; 49(12):1429-1433

Tobacco Use and/or Dependence

Post-index tobacco use and/or dependence was measured using the ICD-9-CM codes 305.1, V15.82, 649.00-649.04, 989.84.[26-28] Tobacco use and/or dependence was dichotomized as either "no" (where no claims for tobacco use and/or dependence exist during the 12-month post-index period) or "yes" (where at least one claim for tobacco use and/or dependence was found during the 12-month post-index period).

Antidepressant Persistence

Antidepressant persistence was operationalized as the number of consecutive days of antidepressant use before a 45-day or greater gap of no antidepressant medication.

STATISTICAL ANALYSIS

Statistical analyses were performed using PASW Statistics 18 (formally SPSS Statistics, Chicago IL), SAS for Windows, Version 9.3 (SAS Institute, Cary, NC), and StataSE 12.0 (StataCorp, College Station, TX). All statistical tests were two-tailed and utilized an a priori significance level of $p<0.05$. Normal distributions and data abnormalities were determined using skewness, kurtosis, frequency, and normality tests.

For Objectives 1-2, descriptive statistics, such as means, standard deviations (SD), and frequencies, were reported for all independent and dependent variables. Other statistical analyses included: Pearson's chi-square test for dichotomous variables, independent samples t-tests for normally-distributed continuous variables, and Mann-Whitney U tests for non-parametric variables.

For Objective 3, logistic regression was utilized to assess the medication adherence variables—MPR and PDC (dichotomized as meeting a threshold of $\geq$ 80% or not). MPR was defined as the sum of the days' supply divided by the number of days in the post-index period. PDC represented the number of days with medication available divided by the number of days in the post-index period.

For Objective 4, Cox proportional hazards regression was used to measure medication persistence defined as the time, in days, until medication nonpersistence occurred. A gap of more than 45 days with no medication indicated nonpersistence. Secondary analyses using 30-day and 60-day gaps were also conducted.

For Objectives 5, logistic regression was also utilized to assess the rates of suicide ideation and suicide attempts post-index.

For Objective 6, generalized linear models associated with count data were used to analyze health care utilization (i.e., psychotic depression-related and all-cause hospitalizations,

hospitalization days, and outpatient/emergency department visits). Although the use of Poisson regression was originally planned, negative binomial regression was utilized instead due to over dispersed data (i.e., mean < variance). Overdispersion is supported by a significant Likelihood Ratio chi-square test of alpha=0. With count data with a high frequency of zeros, zero-inflated negative binomial regression is often utilized. Zero-inflated regression was utilized, specifically, when excessive zeros occurred and were generated from a process distinct from the count value zeros. A significant Vuong test further supports the need for a zero-inflated model. For count variables with a high frequency of zeros generated from the same process as the non-zeros, a hurdle model was utilized instead.[29]

For Objective 7, generalized linear models with a gamma distribution and log-link function were utilized to estimate health care costs (i.e., psychotic depression-related medication costs, psychotic depression-related medical costs, psychotic depression-related total costs, all-cause medication costs, all-cause medical costs, and all-cause total costs). A two-part model (using a logit model and a generalized linear model with a gamma distribution and log-link function) was used for dependent variables with high frequency of $0 costs.

For the descriptive objective (Objective 2), cumulative incidence was calculated as a simple ratio of the total number of new cases of disease during 1-year of follow-up divided by the total number of patients susceptible to disease (i.e., dyslipidemia, diabetes mellitus, and extrapyramidal symptoms) at the index date. For the statistical comparison objective (Objective 8), Cox proportional hazards regression was used to measure the time to disease progression, in days, between cohorts.

Table 2.7 provides a summary of the study objectives, hypotheses, variables, measures, and statistical analyses that were utilized. Each study objective and hypothesis was paired with

the appropriate statistical technique based on the variables of interest (e.g., dichotomous, ordinal, or continuous), data distributions, and overall purpose of the study objective or hypothesis in question.

Table 2.7: Summary of Study Objectives, Hypotheses, Variables, Measures, and Statistical Analyses

Objectives/Hypotheses	Dependent Variable	Measurement Level	Independent Variable	Measurement Level	Statistical Analysis
Objective 1: To describe and compare the baseline socio-demographic and clinical characteristics of Texas Medicaid patients with MD-Psy who utilize either antidepressant monotherapy (AD cohort) or combination therapy with an antidepressant and a second-generation antipsychotic (AD/SGA cohort).	Age	Continuous	Patient Cohort	Dichotomous	Descriptive Statistics & Independent Samples T-Test
	Race/Ethnicity	Categorical			Descriptive Statistics & Pearson's Chi-Square (χ^2)
	Gender	Dichotomous			Descriptive Statistics & Pearson's Chi-Square (χ^2)
	Urban Residence	Dichotomous			Descriptive Statistics & Pearson's Chi-Square (χ^2)
	CCI	Continuous			Descriptive Statistics & Mann-Whitney U
Objective 2: To describe and compare the post-index clinical characteristics of the AD and AD/SGA cohorts.	Tobacco Use and/or Dependence	Dichotomous	Patient Cohort	Dichotomous	Descriptive Statistics & Pearson's Chi-Square (χ^2)
	Antidepressant Persistence (45-day gap)	Continuous			Descriptive Statistics & Independent Samples T-Test
	Cumulative Incidence of Dyslipidemia	Continuous			Descriptive Statistics & Pearson's Chi-Square (χ^2)
	Cumulative Incidence of Diabetes Mellitus	Continuous			Descriptive Statistics & Pearson's Chi-Square (χ^2)
	Cumulative Incidence of Extrapyramidal Symptoms	Continuous			Descriptive Statistics & Pearson's Chi-Square (χ^2)
	[a]Second-Generation Antipsychotic Persistence (45-day gap)	Continuous	N/A	N/A	Descriptive Statistics

Table 2.7: Summary of Study Objectives, Hypotheses, Variables, Measures, and Statistical Analyses (continued)

Objectives/Hypotheses	Dependent Variable	Measurement Level	Independent Variable	Measurement Level	Statistical Analysis
Objective 3: To determine if medication adherence rates (medication possession ratio – MPR and proportion of days covered – PDC) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.					
H_{03A}: The likelihood of being adherent as measured by MPR ≥ 80% to antidepressant therapy does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Medication Adherence (MPR)	Dichotomous	Patient Cohort Covariates[b]	Dichotomous	Logistic Regression
H_{03B}: The likelihood of being adherent as measured by PDC ≥ 80% to antidepressant therapy does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Medication Adherence (PDC)	Dichotomous	Patient Cohort Covariates[b]	Dichotomous	Logistic Regression
Objective 4: To determine if the risk of medication nonpersistence differs between patients in the AD and AD/SGA cohorts, while controlling for covariates.					
H_{04A}: The time, in days, to antidepressant medication nonpersistence (using a 45-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Medication Persistence (Survival Time)	Continuous	Patient Cohort Covariates[b]	Dichotomous	Cox Proportional Hazards Regression
H_{04B}: The time, in days, to antidepressant medication nonpersistence (using a 30-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Medication Persistence (Survival Time)	Continuous	Patient Cohort Covariates[b]	Dichotomous	Cox Proportional Hazards Regression
H_{04C}: The time, in days, to antidepressant medication nonpersistence (using a 60-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Medication Persistence (Survival Time)	Continuous	Patient Cohort Covariates[b]	Dichotomous	Cox Proportional Hazards Regression

Table 2.7: Summary of Study Objectives, Hypotheses, Variables, Measures, and Statistical Analyses (continued)

Objectives/Hypotheses	Dependent Variable	Measurement Level	Independent Variable	Measurement Level	Statistical Analysis
Objective 5: To determine if rates of post-index suicide ideation and suicide attempts differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.					
H_{05A}: The likelihood of having post-index suicide ideation does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Suicide Ideation	Dichotomous	Patient Cohort Covariates[c]	Dichotomous	Logistic Regression
H_{05B}: The likelihood of having a post-index suicide attempt does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Suicide Attempts	Dichotomous	Patient Cohort Covariates[c]	Dichotomous	Logistic Regression
Objective 6: To identify if post-index health care utilization rates (psychotic depression-related hospitalizations, length of psychotic depression-related hospitalization stay, psychotic depression-related outpatient/emergency department visits, all-cause hospitalizations, length of all-cause hospitalization stay, all-cause outpatient/emergency department visits) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.					
H_{06A}: The number of post-index psychotic depression-related hospitalizations does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Number of Psychotic Depression-Related Hospitalizations	Count	Patient Cohort Covariates[c]	Dichotomous	Poisson Regression/ Negative Binomial Regression
H_{06B}: The number of post-index psychotic depression-related hospitalization days (sum of hospital stays, in days) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Number of Psychotic Depression-Related Hospitalization Days	Count	Patient Cohort Covariates[c]	Dichotomous	Poisson Regression/ Negative Binomial Regression
H_{06C}: The number of post-index psychotic depression-related outpatient/emergency department visits does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Number of Psychotic Depression-Related Emergency Department Visits	Count	Patient Cohort Covariates[c]	Dichotomous	Poisson Regression/ Negative Binomial Regression

Table 2.7: Summary of Study Objectives, Hypotheses, Variables, Measures, and Statistical Analyses (continued)

Objectives/Hypotheses	Dependent Variable	Measurement Level	Independent Variable	Measurement Level	Statistical Analysis
H_{06D}: The number of post-index all-cause hospitalizations does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Number of All-Cause Hospitalization Days	Count	Patient Cohort Covariates[c]	Dichotomous	Zero-Inflated Poisson Regression/Zero-Inflated Negative Binomial Regression
H_{06E}: The number of post-index all-cause hospitalization days (sum of hospital stays, in days) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Number of All-Cause Hospitalizations Days	Count	Patient Cohort Covariates[c]	Dichotomous	Zero-Inflated Poisson Regression/Negative Binomial-Logit Hurdle Model Regression
H_{06F}: The number of post-index all-cause outpatient/emergency department visits does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Number of All-Cause Emergency Department Visits	Count	Patient Cohort Covariates[c]	Dichotomous	Poisson Regression/ Negative Binomial Regression
Objective 7: To determine if post-index adjusted health care costs (psychotic depression-related medication, psychotic depression-related medical, psychotic depression-related total, all-cause medication, all-cause medical, and all-cause total costs) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.					
H_{07A}: The post-index psychotic depression-related medication costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Psychotic Depression-Related Medication Costs	Continuous	Patient Cohort Covariates[c]	Dichotomous	GLM with gamma distribution and log-link function
H_{07B}: The post-index psychotic depression-related medical costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Psychotic Depression-Related Medical Costs	Continuous	Patient Cohort Covariates[d]	Dichotomous	GLM with gamma distribution and log-link function
H_{07C}: The post-index psychotic depression-related total costs (psychotic depression-related prescription and psychotic depression-related medical costs) do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Psychotic Depression-Related Costs	Continuous	Patient Cohort Covariates[c]	Dichotomous	GLM with gamma distribution and log-link function

Table 2.7: Summary of Study Objectives, Hypotheses, Variables, Measures, and Statistical Analyses (continued)

Objectives/Hypotheses	Dependent Variable	Measurement Level	Independent Variable	Measurement Level	Statistical Analysis
H_{07D}: The post-index all-cause medication costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	All-Cause Medication Costs	Continuous	Patient Cohort Covariates[c]	Dichotomous	GLM with gamma distribution and log-link function
H_{07E}: The post-index all-cause medical costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	All-Cause Medical Costs	Continuous	Patient Cohort Covariates[c]	Dichotomous	GLM with gamma distribution and log-link function
H_{07F}: The post-index all-cause total costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	All-Cause Total Costs	Continuous	Patient Cohort Covariates[c]	Dichotomous	GLM with gamma distribution and log-link function
Objective 8: To determine if the risks of medication therapy (incident dyslipidemia, incident diabetes mellitus, and incident extrapyramidal symptoms) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.					
H_{08A}: The progression to the first diagnosis of dyslipidemia (after a 45-day post-index period) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Incident Dyslipidemia (Survival Time)	Continuous	Patient Cohort Covariates[c]	Dichotomous	Cox Proportional Hazards Regression
H_{08B}: The progression to the first diagnosis of diabetes mellitus (after a 45-day post-index period) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Incident Diabetes Mellitus (Survival Time)	Continuous	Patient Cohort Covariates[c]	Dichotomous	Cox Proportional Hazards Regression
H_{08C}: The progression to the first diagnosis of extrapyramidal symptoms post-index does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Incident Extrapyramidal Symptoms (Survival Time)	Continuous	Patient Cohort Covariates[c]	Dichotomous	Cox Proportional Hazards Regression

AD = antidepressant monotherapy; **SGA** = second-generation antipsychotic therapy; **CCI** = Charlson comorbidity index; **MPR** = medication possession ratio; **PDC** = proportion of days covered; **GLM** = generalized linear model

[a]Descriptive statistics only and not a dependent variable.

[b]Covariates include: age, race/ethnicity, gender, urban residence, CCI, tobacco use and/or dependence.

[c]Covariates include: age, race/ethnicity, gender, urban residence, CCI, tobacco use and/or dependence, antidepressant persistence.

I. Statistical Test Assumptions and Sample Size Calculations

Statistical test assumptions were checked prior to conducting statistical test analyses. Sample size calculations were also conducted for each statistical test to determine the minimum number of patients needed in order to maintain power of 0.80 and an alpha of 0.05 for all statistical analyses.

II. General Linear Models

General linear models represent a class of statistical methods that maintain two very important characteristics: linearity and additivity. Firstly, linear relationships between variables are assumed, where relationships are represented by a straight line. Secondly, the effects of variables are additive in relation to each other, where for example, the effect of a third variable will add to the predictability of the first and second variables within a prediction equation. General linear model techniques involve bivariate forms (e.g., Pearson's product-moment correlation) and simple multiple forms (e.g., multiple linear regression, logistic regression, or survival analysis).[30]

III. Multiple Linear Regression

Multiple linear regression is a highly utilized general linear model that assesses or predicts the relationship between a dependent variable and at least two independent variables. Multiple regression utilizes the following equation: $Y' = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + {}_k X_k$, where Y' represents the predictor dependent variable score, β_0 is the intercept, X_1 *through* X_k are the independent variables, and k is the total number of independent variables assessed in the model. The β values are the regression coefficients, which represent the magnitude and direction of the

relationship between their corresponding independent variables and the dependent variable being predicted.[30]

Before multiple linear regression can be utilized the following assumptions were tested and met: 1) normal distribution of residuals across the predicted dependent variable scores; 2) linearity between residuals and predicted dependent variable scores; 3) homoscedasticity or the constant variance of the residuals across the predicted dependent variable scores; 4) independence of errors of prediction; and 5) the observations are sampled independently (e.g., as a simple random sample from a large population).[30,31]

Based on G*Power (Version 3.1.7) software, an estimated total sample size of 395 patients was needed to conduct a multiple regression analysis (power=0.80; two-tailed α=0.05; Cohen's small effect size, f^2=0.02;[32] and total number of predictors=8).[33,34]

IV. Logistic Regression

In order to assess Objectives 3 and 5, logistic regression was utilized to predict the dependent variables (or discrete outcomes) from a set of independent variables. Logistic regression utilizes the following equation: ln (odds of Y=1) = $\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + {}_k X_k$, where Y=1 refers to having the outcome of interest (such as being adherent to medications) and the odds of Y=1 is equal to the (probability of Y=1) / (1–(probability of Y=1)). Prior to utilizing logistic regression, the following statistical test assumptions were tested and met: 1) independence of observations; 2) linear relationship between the independent variables and the logit transformed dependent variable (e.g., assumption met by failing to reject the null hypothesis for the Hosmer and Lemeshow goodness-of-fit test); 3) independence of errors of prediction; and 4) adequate power (i.e., large enough sample size).[30]

Using G*Power (Version 3.1.7) software, a minimum total sample size of 4842 patients was calculated based on the following: power=0.80; two-tailed α=0.05; a conservative estimate of the probability of an event, $Pr(Y=1|X=1)H_0=0.05$, based on the literature (range: 9.4% to 21.8%);[35,36] a range of odds ratios (OR=1.5 to 5.0); and a binomial independent variable distribution with 50% on AD/SGA therapy.[33,34] Table 2.8 provides the range of estimated sample sizes needed to conduct a logistic regression analysis.

Table 2.8: Estimated Sample Sizes for Logistic Regression

Odds Ratio	1.5	2.5	5.0
R-squared[a]	0.1	0.1	0.1
Total Sample Size	3766	615	166
Odds Ratio	1.5	5.0	5.0
R-squared[a]	0.2	0.2	0.2
Total Sample Size	4237	692	187
Odds Ratio	1.5	5.0	5.0
R-squared[a]	0.3	0.3	0.3
Total Sample Size	**4842**	791	213

Probability $(Y=1|X=1)H_0=0.05$; two-tailed α=0.05; power=0.80; binomial distribution with 50% patients on AD/SGA therapy.
[a]Represents the value obtained when X_1 is regressed over the other independent variables in the regression model.

V. Cox Proportional Hazards Regression

In order to assess Objectives 4 and 8, survival analysis, specifically the Cox proportional hazards regression method, was employed. Survival analysis is a type of statistical technique that measures the time until a certain event, such as medication nonpersistence or the development of medication-related adverse events (e.g., dyslipidemia, diabetes mellitus, and extrapyramidal symptoms). In Cox proportional hazards regression, the dependent variable is measured as survival time and is measured in relation to one or more covariates (or independent variables).[30]

Cox proportional hazards regression utilizes the following equation: $\log[\lambda(t|X)/\lambda_0(t)] = \Phi_1X_1 + \Phi_2X_2 + \ldots \Phi_kX_k$, where $\lambda(t)$ represents the hazard function for survival time T, $\lambda_0(t)$ is the baseline hazard, and X represent the independent variables.[37] When using regression with survival analysis, the assumptions similar to multiple linear regression are not required; however, meeting the assumptions of multivariate normality, linearity, and homoscedasticity may increase the power of the analysis. In order to utilize survival analysis methods, the following assumptions were tested and met: 1) lack of systematic error between censored and remaining cases; 2) lack of change in survival conditions over time; and 3) the shape of the survival function is constant across cases and groups over time.[30]

Using StataSE 12.0 software, a minimum total sample size of 3411 patients was calculated based on the following: power=0.80; two-tailed α=0.05; a log Hazard ratio range of B=1.5-2.0; and an estimated range of the probability of an event based on the literature, $Pr(Y=1|X=1)H_0$=0.08 to 0.50.[38] Table 2.9 provides the range of estimated sample sizes needed to conduct a Cox proportional hazards regression analysis.

Table 2.9: Estimated Sample Sizes for Cox Proportional Hazards Regression

B (log Hazard ratio)[a]	1.5	1.5	1.5	1.5
P (Overall Event Rate)[b]	0.08	0.10	0.3	0.5
R-squared[c]	0.1	0.1	0.1	0.1
Total Sample Size	2653	2122	708	425
B (log Hazard ratio)[a]	1.5	1.5	1.5	1.5
P (Overall Event Rate)[b]	0.08	0.10	0.3	0.5
R-squared[c]	0.2	0.2	0.2	0.2
Total Sample Size	2984	2388	796	478
B (log Hazard ratio)[a]	1.5	1.5	1.5	1.5
P (Overall Event Rate)[b]	0.08	0.10	0.3	0.5
R-squared[c]	0.3	0.3	0.3	0.3
Total Sample Size	**3411**	2729	910	546
B (log Hazard ratio)[a]	2.0	2.0	2.0	2.0
P (Overall Event Rate)[b]	0.08	0.10	0.3	0.5
R-squared[c]	0.1	0.1	0.1	0.1
Total Sample Size	908	727	243	146
B (log Hazard ratio)[a]	2.0	2.0	2.0	2.0
P (Overall Event Rate)[b]	0.08	0.10	0.3	0.5
R-squared[c]	0.2	0.2	0.2	0.2
Total Sample Size	1022	817	273	164
B (log Hazard ratio)[a]	2.0	2.0	2.0	2.0
P (Overall Event Rate)[b]	0.08	0.10	0.3	0.5
R-squared[c]	0.3	0.3	0.3	0.3
Total Sample Size	1167	934	312	187

Probability $(Y=1|X=1)H_0=0.08$-0.50; two-tailed $\alpha=0.05$; power=0.80; binomial distribution with 50% patients on AD/SGA therapy

[a]Regression coefficient or the predicted change in log(base e) hazards as X_1 changes by one unit, holding constant all other independent variables. [b]Represents the proportion of patients in which the events occur during a 12-week follow-up period (based on the literature). [c]Represents the value obtained when X_1 is regressed over the other independent variables in the regression model.

VI. Cumulative Incidence

Incidence is measured in cohort studies, where the basic equation used to measure incidence is a ratio of the total number of events that occurred in a specific population over a defined time period (numerator) by the total number of people in the population at risk during that same time period (denominator). Incidence can be measured based on either (1) incidence based on persons at risk or (2) incidence based on person-time units at risk, where the units of measurement in the denominator determine which type of incidence measurement is utilized. When persons in the population provide different follow-up periods, incidence based on person-time units at risk should be utilized. However, when the follow-up period is complete or the same for each person, incidence based on individuals at risk is employed, where the cumulative incidence (also known as the incidence proportion) is calculated.[39]

For Objective 2, cumulative incidence was calculated as the number of new cases of disease (i.e., dyslipidemia, diabetes mellitus, and extrapyramidal symptoms) that occurred during the one-yr follow-up period divided by the total number of susceptible cases without the disease at the index date during the one-yr follow-up period. Before utilizing cumulative incidence in survival analysis, the assumptions associated with Cox proportional hazards regression (listed above) were tested and met.

VII. Generalized Linear Models

Generalized linear models (GLMs) also represent a sizeable class of statistical models that utilize a theoretical framework, allowing for simplified implementation and flexibility during data analysis.[40] GLMs have three components: a random component, a linear predictor, and a linearizing link function.[31,41]

The random component of a GLM specifies the conditional distribution of the dependent variable (Y_i) based on the values of the independent variables in the model.[31] The distribution of Y_i may consist of a normal distribution or other distributions in the exponential family such as Gaussian, inverse-Gaussian, Poisson, negative binomial, gamma, or beta distributions.[31,40] For example, Gaussian distributions are variant distributions of the standard bell curve, where a normal curve represents one type of a Gaussian distribution. Count data generally follow Poisson distributions, and as the samples grow, the distributions will approximate a normal distribution. Gamma distributions are continuous positive distributions, where the variance of the dependent variable increases as its mean increases.[31]

The second component of a GLM is the linear predictor, which represents the linear function of regressors, as described in the equation: $\eta_i = \alpha + \beta_1 X_{i1} + \beta_2 X_{i2} + \ldots + \beta_k X_{ik}$. Regressors ($X_{ij}$) are pre-specified functions of independent variables that may be, for example, quantitative, transformed, dummy-coded, or even represented as interactions.[31]

The third component of a GLM is the linearizing link function, $g(\cdot)$, which allows transformation of the expected dependent variable, $\mu_i \equiv E(Y_i)$, to the following linear predictor: $g(\mu_i) = \eta_i = \alpha + \beta_1 X_{i1} + \beta_2 X_{i2} + \ldots + \beta_k X_{ik}$. The linearizing link function is smooth and invertible in nature allowing for the linear transformation of a non-linear dependent variable (or nonlinear regression), where the equation is transformed into the following: $\mu_i = g^{-1}(\eta_i) = g^{-1}(\alpha + \beta_1 X_{i1} + \beta_2 X_{i2} + \ldots + \beta_k X_{ik})$. The use of a certain link function is dependent on the range of the

distribution of the dependent variable.[31] Table 2.10 displays examples of exponential families and their canonical link functions and the dependent variable range of responses.

Table 2.10: Exponential Families and Corresponding Canonical Links, Response Ranges, and Conditional Variance Functions

Family	Canonical Link	Range of Y_i	$V(Y_i\|\eta_i)$
Gaussian	Identity	$(-\infty, +\infty)$	Φ
Binomial	Logit	$(0,1,\ldots,n_i) / (n_i)$	$\mu_i(1-\mu_i) / n_i$
Poisson	Log	0, 1, 2, …	μ_i
Gamma	Inverse	$(0, \infty)$	$\Phi \mu^2_i$
Inverse-Gamma	Inverse-square	$(0, \infty)$	$\Phi \mu^3_i$

Adapted from: Generalized Linear Models. In Fox J., *Applied Regression Analysis and Generalized Linear Models*. 2nd ed. Chapter 15. Thousand Oaks, CA: Sage Publications, 2008.[31]

Key assumptions that were tested and met prior to utilizing GLMs included: 1) independence of observations; 2) correct model specification in relation to the link and variance functions; 3) correct measurement scale for the independent variables; and 4) lack of influence of outliers or other individual observations on the fitted model.[42]

Generalized Linear Model with Negative Binomial and Gamma Distributions

In order to assess Objectives 6 and 7, GLMs were utilized. Specifically, generalized linear models (negative binomial regression, zero-inflated negative binomial regression, and negative binomial-logit hurdle model regression) were employed for Objective 6 since the dependent variables were overdispersed count variables with or without excess zeros. A GLM with a gamma distribution and log-link function was utilized for Objective 7 to evaluate health care costs.[43,44]

Using G*Power (Version 3.1.7) software, a minimum total sample size of 102 patients was calculated based on the following: power=0.80, two-tailed α=0.05, $\text{Exp}(\beta_1)$=1.10 (to detect a

10% difference in health care utilization),[45] a mean exposure of 365 days, a binomial independent variable distribution with 50% on AD/SGA therapy, and a baseline health care utilization rate (i.e., suicide attempts and hospitalizations) range of 10% to 25% based on the literature.[33,34,46,47] Table 2.11 provides the range of estimated sample sizes needed to conduct negative binomial regression based on a Poisson-distributed GLM.

Table 2.11: Estimated Sample Sizes for Poisson-Distributed GLM

Base Rate	0.10	0.15	0.20	0.25
R-squared[a]	0.1	0.1	0.1	0.1
Total Sample Size	80	53	51	32
Base Rate	0.10	0.15	0.20	0.25
R-squared[a]	0.2	0.2	0.2	0.2
Total Sample Size	89	60	45	36
Base Rate	0.10	0.15	0.20	0.25
R-squared[a]	0.3	0.3	0.3	0.3
Total Sample Size	**102**	68	51	41

$\text{Exp}(\beta_1)=1.10$; two-tailed $\alpha=0.05$; power=0.80; binomial distribution with 50% patients on AD/SGA therapy

[a]Represents the value obtained when X1 is regressed over the other independent variables in the regression model

Moran and associates[48] reported that appropriately specified GLMs may more closely model the error structure of cost data compared to traditional models of ordinary least squares regression that utilize log-transformed costs. Although there is a dearth of literature pertaining to power analyses for GLMs with a gamma distribution and log-link function, Jin and Zhao[49] support that the sample size needed for a gamma distribution will not be greater than the sample size required for a normal distribution at the same power level. Therefore, G*Power (Version 3.1.7) software was used to calculate the minimum size needed when employing a GLM with a gamma distribution and log-link function. A sample size based on multiple linear regression was calculated, and an estimated total sample size of 395 patients was needed (power=0.80; two-tailed α=0.05; Cohen's small effect size, f^2=0.02;[32] and total number of predictors=8).[33,34]

Based on the estimated sample sizes for each statistical analysis (i.e., multiple linear regression, logistic regression, Cox proportional hazards regression, and negative binomial and gamma-distributed GLMs), the minimum overall sample size of **4842** patients was required for the present study.

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Chapter 3: Results

Chapter Overview

This chapter provides a description of the study results. Details regarding the patient selection process, patient socio-demographics, and patient clinical characteristics are presented. The study objectives, hypotheses, and statistical analysis results are also provided.

Extraction of Eligible Patients

From September 2007 through December 2012, a total of 28,049 patients had at least one diagnosis for severe major depressive disorder with psychotic features. Of those patients, 7,148 (25.5%) had no prescription claims for an antidepressant medication. Therefore, the remaining 20,901 patients were assessed for the study inclusion and exclusion criteria in order to determine the final sample.

The final sample size included 926 patients (3.3%) and two study cohorts. Of the final sample, there were 510 patients in the antidepressant monotherapy (AD) cohort and 416 patients in the antidepressant plus second-generation antipsychotic (AD/SGA) cohort. The study inclusion and exclusion criteria, as well as the resulting sample sizes, are provided in Table 3.1. During the post-index period, SSRI therapy accounted for almost half of the antidepressant prescription claims (46.0%). For the AD/SGA cohort, the top three utilized SGA medications were risperidone (29.0%), quetiapine (27.4%), and aripiprazole (22.3%). The antidepressant and second-generation medication claims for the final sample are presented in Tables 3.2 and 3.3.

Table 3.1: Patient Selection in Texas Medicaid Database

Study Criteria	Subjects Excluded		Subjects Remaining	
	N	%	N	%
Initial Sample			28,049	100.0
No claims for an antidepressant medication[a]	7,148	25.5	20,901	74.5
Did not have the 6-month pre-index and 12-month post-index periods of continuous enrollment	14,172	50.5	6,729	24.0
No diagnosis for psychotic depression during pre-index or post-index periods	2,667	9.5	4,062	14.5
Had a claim for electroconvulsive therapy during pre-index or post-index periods	8	0.0	4,054	14.5
Had at least one diagnosis for confounding disease state(s):	2,027	7.2	2,027	7.2
Bipolar disorder[b]	1,429			
Schizophrenia	929			
Mental retardation	203			
Other cerebral degenerations	84			
Dementia	65			
Pervasive development disorder	42			
Parkinson's disease	12			
Senility without psychosis	1			
Did not have at least two post-index antidepressant medication claims	321	1.1	1,706	6.1
Had a claim for clozapine during pre-index or post-index periods	0	0.0	1,706	6.1
Had a claim for an FGA during pre-index or post-index periods	164	0.6	1,542	5.5
Had a claim for an SGA during pre-index period	175	0.6	1,367	4.9
Did not have at least two post-index SGA medication claims	153	0.5	1,214	4.3
Did not have overlap of ≥30-day if on antidepressant and SGA therapy	25	0.1	1,189	4.2
Did not start first SGA on index date	263	0.9	926	3.3
Final Sample			**926**[d]	

FGA = first-generation antipsychotic; **SGA** = second-generation antipsychotic
[a]During period of September 1, 2007 to December 31, 2012
[b]Also includes manic depression and cyclothymic disorder
[c]Final sample: AD cohort = 510 patients; AD/SGA cohort = 416 patients

Table 3.2: Antidepressant Medication Prescription Claims by Medication Class

Antidepressant Medications	Number of Claims	%
SSRI	**3,055**	**46.0**
Citalopram	843	12.7
Escitalopram	604	9.1
Fluoxetine	552	8.3
Fluvoxamine	32	0.5
Paroxetine	169	2.5
Sertraline	855	12.9
SSRI & Partial Agonist	**27**	**0.4**
Vilazodone	27	0.4
SNRI	**1,199**	**18.0**
Desvenlafaxine	185	2.8
Duloxetine	669	10.1
Venlafaxine	345	5.2
Aminoketone	**580**	**8.7**
Buproprion	580	8.7
Triazolopyridines	**1,131**	**17.0**
Trazodone	1,131	17.0
Tetracyclines	**342**	**5.1**
Mirtazapine	342	5.1
TCA	**309**	**4.7**
Amitriptyline	202	3.0
Amoxapine	1	0.0
Doxepin	72	1.1
Imipramine	8	0.1
Nortriptyline	26	0.4
Total	**6,643**	**99.9**[a]

SSRI = selective serotonin reuptake inhibitor; **SNRI** = serotonin-norepinephrine reuptake inhibitor; **TCA**= tricyclic antidepressant

[a]Total does not equal 100.0 due to rounding error

Table 3.3: Second-Generation Antipsychotic Prescription Claims by Medication

Second-Generation Antipsychotic[a]	Number of Claims	%
Asenapine	4	0.2
Aripiprazole	573	22.3
Lurasidone	3	0.1
Olanzapine[b]	197	7.7
Paliperidone	136	5.3
Risperidone	748	29.0
Quetiapine	705	27.4
Ziprasidone[c]	209	8.1
Total	**2575**	**100.1[d]**

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Represents oral and injectable medications
[b]Includes olanzapine and fluoxetine combination product (Symbyax)
[c]Includes one medical claim for Geodon® injection
[d]Total does not equal 100.0 due to rounding error

DESCRIPTIVE STATISTICS

Baseline socio-demographic and clinical characteristics were calculated for the final study sample. Results are presented in Table 3.4.

BASELINE SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF FINAL SAMPLE

Of the final sample, the majority of patients were aged 35 years or older (64.0%). Females (66.8%) represented the majority of patients based on gender, and most patients were of either Caucasian (25.2%), African American (34.9%), or Hispanic (36.7%) race/ethnicity. Urban dwellers comprised 79.5% of the final sample, and over two-thirds (68.9%) had no comorbidities based on the Charlson Comorbidity Index score.

Table 3.4: Baseline Summary Statistics for Final Sample

Socio-Demographics	N	%
Age groups (years)		
18-24	156	16.8
25-34	177	19.1
35-44	144	15.6
45-54	309	33.4
55-63	140	15.1
Total	**926**	**100.0**
Gender		
Female	619	66.8
Male	307	33.2
Total	**926**	**100.0**
Race/Ethnicity		
Caucasian	233	25.2
African American	323	34.9
Hispanic	340	36.7
Other[a]	30	3.2
Total	**926**	**100.0**
Urban Residence		
Yes	736	79.5
No	190	20.5
Total	**926**	**100.0**
Clinical Characteristic	**N**	**%**
Charlson Comorbidity Index (CCI)		
0	638	68.9
1	143	15.4
2	75	8.1
3-4	47	5.1
>4	23	2.5
Total	**926**	**100.0**

[a]Other includes: Asian and Unknown

STUDY OBJECTIVES

I. Objective 1: Description and Comparison of Baseline Characteristics

The purpose of Objective 1 was to describe and compare the baseline socio-demographic and clinical characteristics of Texas Medicaid patients with MD-Psy who utilized either antidepressant monotherapy (AD cohort) or combination therapy with an antidepressant and a second-generation antipsychotic (AD/SGA cohort). Table 3.5 provides the comparison of baseline socio-demographic and clinical characteristics between the AD and AD/SGA cohorts.

On average, compared to the AD/SGA cohort, the AD cohort was significantly younger ($p=0.001$) and had more comorbidities based on the Charlson Comorbidity Index score ($p<0.001$). There was a significant difference in relation to race/ethnicity ($p<0.001$), where the AD cohort had larger proportions of Caucasians and Hispanics, compared to the AD/SGA cohort. Finally, the AD/SGA cohort had significantly less females ($p<0.001$) and rural dwellers ($p<0.001$), compared to the AD cohort.

Table 3.5: Comparison of Baseline Characteristics by Cohort

	AD (N=510)	AD/SGA (N=416)	p-value
Age, Mean (±SD)[a]	39.2 (±13.3)	42.0 (±13.0)	0.001*
Gender (%)[b]			<0.001*
Female	72.2	60.3	
Male	27.8	39.7	
Race/Ethnicity (%)[b]			<0.001*
Caucasian	30.0	19.2	
African American	28.0	43.3	
Hispanic	39.2	33.7	
Other[c]	2.7	3.8	
Urban Residence (%)[b]			<0.001*
No	25.7	14.2	
Yes	74.3	85.8	
Charlson Comorbidity Index[d]			<0.001*
Median	0.0	0.0	
Mean (±SD)	0.8 (±1.4)	0.5 (±1.2)	

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Independent samples t-test
[b]Pearson's Chi-square
[c]Other includes: Asian, Unknown
[d]Mann-Whitney U
*Significant at p<0.05

II. Objective 2: Description and Comparison of Post-Index Clinical Characteristics

The purpose of Objective 2 was to describe and compare the post-index clinical characteristics of the AD and AD/SGA cohorts. Table 3.6 and 3.7 provide descriptions and comparisons of the post-index clinical characteristics between cohorts.

Overall, the cumulative incidences of dyslipidemia were 20.5% and 17.0% for the AD cohort and the AD/SGA cohort, respectively. Compared to dyslipidemia, the cumulative incidences of diabetes mellitus were lower for both cohorts (6.8% for the AD cohort versus 6.3% for the AD/SGA cohort). The cumulative incidences were even lower for extrapyramidal symptoms at 1.6% (AD cohort) and 1.0% (AD/SGA cohort). There were no significant differences between the number of new cases of dyslipidemia, diabetes mellitus, or extrapyramidal symptoms between cohorts.

There was no significant difference between the two cohorts regarding tobacco use or dependence post-index ($p=0.074$). On average, compared to the AD cohort, the antidepressant persistence rate using a 45-day permissible gap was significantly longer for the AD/SGA cohort by approximately 34 days ($p<0.001$). The combination cohort's SGA persistence rate using a 45-day permissible gap had a mean (±SD) of 178.6 (±127.9) days, where almost half of the AD/SGA cohort (49.3%) utilized SGA therapy for five months or longer.

Table 3.6: Description of Post-Index Characteristics by Cohort

Clinical Characteristics	AD (N=510)		AD/SGA (N=416)	
	N	%	N	%
Dyslipidemia				
Yes	79	20.5	55	17.0
No	306	79.5	269	83.0
Total[a]	**385**	**100.0**	**324**	**100.0**
Diabetes Mellitus				
Yes	27	6.8	22	6.3
No	372	93.2	329	93.7
Total[a]	**399**	**100.0**	**351**	**100.0**
Extrapyramidal Symptoms				
Yes	8	1.6	4	1.0
No	495	98.4	408	99.0
Total[a]	**503**	**100.0**	**412**	**100.0**
Tobacco Use/Dependence				
Yes	111	21.8	71	17.1
No	399	78.2	345	82.9
Total	**510**	**100.0**	**416**	**100.0**
AD Persistence (days)[b]				
0-30	117	22.9	66	15.9
31-90	106	20.8	75	18.0
91-150	88	17.3	57	13.7
>150	199	39.0	218	52.4
Total	**510**	**100.0**	**416**	**100.0**
SGA Persistence (days)[c]				
0-30	--	--	71	17.1
31-90	--	--	80	19.2
91-150	--	--	60	14.4
>150	--	--	205	49.3
Total	**N/A**	**N/A**	**416**	**100.0**

AD = antidepressant; **SGA** = second-generation antipsychotic

[a]Represents the number of patients susceptible to the disease at index

[b]Persistence calculated using a 45-day permissible gap

[c]Applicable to the AD/SGA cohort only

Table 3.7: Comparison of Post-Index Clinical Characteristics by Cohort

	AD (N=510)	AD/SGA (N=416)	p-value
Dyslipidemia Incidence (%)[a,b]	20.5	17.0	0.230
Diabetes Mellitus Incidence (%)[a,b]	6.8	6.3	0.783
Extrapyramidal Symptoms (%)[a,b]	1.6	1.0	0.412
Tobacco Use/Dependence (%)[b]	21.8	17.1	0.074
AD Persistence (45-day gap)[c]			
Mode	30	365	
Median	104	166	
Mean (±SD)[d]	156.8 (±127.1)	191.3 (±132.1)	<0.001*
SGA Persistence (45-day gap)[e]			
Mode		365	
Median		149.5	
Mean (±SD)		178.6 (±127.9)	

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Incidence = new cases of disease / total susceptible to disease at index
[b]Pearson's chi-square
[c]Independent samples t-test
[d]Significant difference between cohorts at p<0.001
[e]SGA therapy used by the AD/SGA group only
*Significant at p<0.05

III. Objective 3: Antidepressant Adherence Based on MPR and PDC

The purpose of Objective 3 was to determine if the rates of antidepressant medication adherence (medication possession ratio – MPR and proportion of days covered – PDC) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates. Therefore, two logistic regression analyses were employed with the dependent variables being MPR (not adherent was MPR < 80%; adherent was MPR ≥ 80%) and PDC (not adherent was PDC < 80%; adherent was PDC ≥ 80%). The primary independent variable being assessed was the study cohort (AD versus AD/SGA). The study covariates utilized in both models included: age, gender, race/ethnicity, urban residence, Charlson Comorbidity Index score, and tobacco use and/or dependence. Multicollinearity, or high correlations among independent variables, was assessed using multiple linear regression analyses. Collinearity statistics showed that tolerance values ranged from 0.565 to 0.960 and variance inflation factor values (calculated as the inverse of tolerance) ranged from 1.042 to 1.771. Since the values for tolerance and variance inflation factor for each independent variable were above 0.1 and below 10, respectively, multicollinearity was not a statistical issue of concern. Table 3.8 provides descriptions and comparisons of the antidepressant adherence measures (MPR and PDC) between cohorts.

Table 3.8: Description and Comparison of Antidepressant Adherence Measures (MPR and PDC) Among Cohorts (N=926)

	AD (N=510)	AD/SGA (N=416)	p-value
MPR (%)[a]			
Adherent (≥80%)	34.1	43.5	0.003*
PDC (%)[a]			
Adherent (≥80%)	28.4	38.7	0.001*

AD = antidepressant; **SGA** = second-generation antipsychotic; **MPR** = medication possession ratio; **PDC** = proportion of days covered

[a]Pearson's chi-square

*Significant at $p<0.05$

Of the final sample, 355 patients (38.3%) were adherent to their antidepressant medication therapy based on MPR. A Hosmer and Lemeshow Goodness of Fit test yielded a non-significant p-value indicating good model fit with the data ($\chi^2=8.591$; df=8; p=0.378). Table 3.9 displays the results of the logistic regression analysis assessing the likelihood of antidepressant adherence based on MPR. A chi-square test comparing the full model (i.e., model includes all covariates) to the constant model (i.e., model contains no covariates) was significant ($\chi^2=80.774$; df=9; $p<0.001$), indicating that at least one covariate was related to the outcome. Compared to patients on antidepressant therapy only, the odds of being adherent to antidepressant medication therapy was 42.0% significantly higher for patients utilizing both an antidepressant and second-generation antipsychotic therapy (OR=1.420; 95% CI=1.062-1.898; p=0.018), while controlling for other variables in the model. Age was also a significant positive predictor, where the odds of being adherent increased significantly by 4.4% as age increased by one year (OR=1.044; 95% CI=1.031-1.056; $p<0.001$). Compared to Caucasian patients, African Americans (OR=0.649; 95% CI=0.448-0.938; p=0.021) had a significantly lower likelihood of being adherent to antidepressant therapy. Compared to non-tobacco users/dependents, the odds

of being adherent based on MPR were significantly lower by about 33.1% for tobacco users/dependents (OR=0.669; 95% CI=0.467-0.959; p=0.029). However, gender, being of Hispanic ethnicity, being of other race, urban residence, and Charlson Comorbidity Index score were not significantly related to adherence based on MPR.

Of the final sample, 306 patients (33.0%) were adherent to their antidepressant medication therapy based on PDC. A Hosmer and Lemeshow Goodness of Fit test yielded a non-significant p-value indicating good model fit with the data (χ^2=6.287; df=8; p=0.615). Table 3.10 displays the results of the logistic regression analysis assessing the likelihood of antidepressant adherence based on PDC. A chi-square test comparing the full model (i.e., model includes all covariates) to the constant model (i.e., model contains no covariates) was significant (χ^2=74.295; df=9; p<0.001), indicating that at least one covariate was related to the outcome. For PDC, the results were very similar to MPR. Compared to patients on antidepressant therapy only, the odds of being adherent to antidepressant medication therapy based on PDC was 52.3% significantly higher for patients utilizing both an antidepressant and second-generation antipsychotic therapy (OR=1.523; 95% CI=1.129-2.053; p=0.006), while controlling for other variables in the model. Age (OR=1.039; 95% CI=1.027-1.052; p<0.001) was also a significant positive predictor of adherence to antidepressant therapy. Compared to Caucasians, African Americans (OR=0.612; 95% CI=0.419-0.894; p=0.011) had a significantly lower likelihood of antidepressant adherence. Compared to non-tobacco users/dependents, the odds of being adherent based on PDC were significantly lower by over 36.4% for tobacco users/dependents (OR=0.636; 95% CI=0.437-0.927; p=0.019). Gender, being of Hispanic ethnicity, being of other race, urban residence, and Charlson Comorbidity Index score were not significant predictors of adherence based on PDC.

H_{03A}: The likelihood of being adherent as measured by MPR ≥ 80% to antidepressant therapy does not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Rejected]**

H_{03B}: The likelihood of being adherent as measured by PDC ≥ 80% to antidepressant therapy does not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Rejected]**

Table 3.9: Logistic Regression Analysis Comparing the Likelihood of Antidepressant Adherence Based on MPR ≥ 80% Among Cohorts (N=926)

	Odds Ratio	95% Confidence Interval		Wald X^2	p-value
Cohort					
AD/SGA	1.420	1.062	1.898	5.596	0.018*
Covariates					
Age	1.044	1.031	1.056	51.360	<0.001*
Female	0.922	0.684	1.242	0.285	0.594
African American	0.649	0.448	0.938	5.290	0.021*
Hispanic	0.800	0.548	1.168	1.336	0.248
Other[a]	1.363	0.607	3.060	0.564	0.453
Urban Residence	0.758	0.528	1.089	2.249	0.134
Charlson Comorbidity Index	0.940	0.841	1.051	1.183	0.277
Tobacco Use/Dependence	0.669	0.467	0.959	4.788	0.029*

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown
*Significant at p<0.05

Table 3.10: Logistic Regression Analysis Comparing the Likelihood of Antidepressant Adherence Based on PDC ≥ 80% Among Cohorts (N=926)

	Odds Ratio	95% Confidence Interval		Wald X^2	p-value
Cohort					
AD/SGA	1.523	1.129	2.053	7.606	0.006*
Covariates					
Age	1.039	1.027	1.052	39.506	<0.001*
Female	0.827	0.610	1.121	1.494	0.222
African American	0.612	0.419	0.894	6.462	0.011*
Hispanic	0.744	0.505	1.096	2.242	0.134
Other[a]	1.232	0.552	2.748	0.259	0.611
Urban Residence	0.738	0.509	1.069	2.580	0.108
Charlson Comorbidity Index	0.919	0.817	1.034	1.957	0.162
Tobacco Use/Dependence	0.636	0.437	0.927	5.546	0.019*

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown
*Significant at p<0.05

IV. Objective 4: Antidepressant Nonpersistence

The purpose of Objective 4 was to determine if the risk of antidepressant medication nonpersistence differs between patients in the AD and AD/SGA cohorts, while controlling for covariates. Therefore, three Cox proportional hazards regression models were employed with the continuous dependent variables being persistence using a 45-day permissible gap (primary analysis), persistence using a 30-day permissible gap (secondary analysis), and persistence using a 60-day permissible gap (secondary analysis). The primary independent variable was the study cohort (AD vs. AD/SGA), and the covariates were age, gender, race/ethnicity, urban residence, Charlson Comorbidity Index score, and tobacco use and/or dependence. Patients were censored if they continued antidepressant medication use through the last day of the post-index period (i.e., day 365).

Prior to utilizing statistical analyses, multicollinearity was assessed and found to be absent based on the tolerance and variance inflation factor scores. The proportionality of hazards assumption for Cox proportional hazards regression requires that each case (and thus each treatment cohort) has the same shape in relation to survival function over time. Essentially, there can be no interactions between treatment cohorts (or other covariates) and time. Proportionality of hazards can be tested by adding all time-dependent interactions to the original model. If any interactions are significant then the assumption has been violated.[1] No significant interactions were found. Therefore, the proportionality of hazards assumptions were met for persistence with a 45-day gap (Wald χ^2=7.114, df=9, p=0.625), persistence with a 30-day gap (Wald χ^2= 7.606, df=9, p=0.574), and persistence with a 60-day gap (Wald χ^2= 13.130, df=9, p=0.157). Table 3.11 provides descriptions and comparisons of the antidepressant persistence rates between cohorts.

Table 3.11: Description and Comparison of Antidepressant Persistence Rates Among Cohorts (N=926)

	AD (N=510)	AD/SGA (N=416)	p-value
AD Persistence (45-day gap)			
Mode	30	365	
Median	104	166	
Mean (±SD)[a]	156.8 (±127.1)	191.3 (±132.1)	<0.001*
AD Persistence (30-day gap)			
Mode	30	30	
Median	90	112.5	
Mean (±SD)[a]	130.7 (±115.4)	158.9 (±126.6)	<0.001*
AD Persistence (60-day gap)			
Mode	365	365	
Median	126	207	
Mean (±SD)[a]	174.8 (±130.9)	216.2 (±133.9)	<0.001*

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Independent samples t-test
*Significant at $p<0.05$

Using persistence with a 45-day gap, the mean survival time (±SD) prior to antidepressant medication nonpersistence was 172.3 days (±130.4). For the AD cohort, the mean survival time (±SD) was 156.8 (±127.1), and for the AD/SGA cohort, the mean survival time (±SD) was 191.3 (±132.1). Table 3.12 provides the results for the Cox proportional hazards regression model using persistence with a 45-day permissible gap, where medication nonpersistence was established when a gap period >45 days between any two consecutive medication fills occurred. The global null hypothesis test was significant (χ^2=69.965; df=9; $p<0.001$), indicating the rejection of the null hypothesis that all coefficients are equal to zero.

The primary variable of interest was significant, where the hazard of antidepressant nonpersistence for the AD/SGA cohort was about 23.2% significantly lower than the hazard for those in the AD cohort (HR=0.768; 95% CI=0.659-0.896; p=0.001), while controlling for other variables in the model. As age increased by one year, the hazard of nonpersistence significantly

decreased by approximately 1.8% (HR=0.982; 95% CI=0.976-0.988; p<0.001). Compared to Caucasian patients, the hazards of medication nonpersistence was significantly higher by about 45.5% for African Americans (HR=1.455; 95% CI=1.192-1.776; p<0.001) and 30.1% for Hispanics (HR=1.301; 95% CI=1.061-1.594; p=0.011). Compared to non-tobacco users/dependents, the hazard of antidepressant nonpersistence was significantly higher by 24.9% in tobacco users/dependents, while controlling for the other covariates in the model (HR=1.249; 95% CI=1.040-1.501; p=0.017). The remaining covariates were not significantly related to the dependent variable.

H_{04A}: The time, in days, to antidepressant medication nonpersistence (using a 45-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Rejected]**

Table 3.12: Cox Proportional Hazards Regression Model Comparing Survival Time (Persistence Using a 45-Day Gap) Prior to Antidepressant Medication Nonpersistence Among Cohorts (N=926)

	Hazard Ratio	95% Hazard Ratio Confidence Interval		Wald X^2	p-value
Cohort					
AD/SGA	0.768	0.659	0.896	11.283	0.001*
Covariates					
Age	0.982	0.976	0.988	36.684	<0.001*
Female	1.025	0.876	1.200	0.097	0.755
African American	1.455	1.192	1.776	13.613	<0.001*
Hispanic	1.301	1.061	1.594	6.408	0.011*
Other[a]	1.204	0.783	1.852	0.713	0.398
Urban Residence	1.133	0.934	1.375	1.610	0.205
Charlson Comorbidity Index	1.010	0.956	1.067	0.124	0.725
Tobacco Use/Dependence	1.249	1.040	1.501	5.678	0.017*

AD = antidepressant; **SGA** = second-generation antipsychotic

[a]Other includes: Asian, Unknown

*Significant at $p<0.05$

Cox Proportional Hazards regression secondary analyses were employed using persistence with a 30-day permissible gap and persistence with a 60-day permissible gap. Results of the analyses are provided in Tables 3.13 and 3.14. Similarly to the regression model using persistence with a 45-day gap, both secondary models were significant in relation to cohort, age, African American race, and Hispanic ethnicity ($p<0.05$). Persistence with a 30-day gap matched the results of the first model, where tobacco use and/or dependence was related to significantly worse hazards of medication nonpersistence (HR=1.270; 95% CI=1.058-1.524; p=0.010). Interestingly, using persistence with a 60-day gap, urban dwellers had a significantly higher hazard of medication nonpersistence by approximately 22.7%, compared to rural dwellers (HR=1.227; 95% CI=1.004-1.499; p=0.046).

H_{04B}: The time, in days, to antidepressant medication nonpersistence (using a 30-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Rejected]**

H_{04C}: The time, in days, to antidepressant medication nonpersistence (using a 60-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Rejected]**

Table 3.13: Secondary Analysis—Cox Proportional Hazards Regression Model Comparing Survival Time (Persistence Using a 30-Day Gap) Prior to Antidepressant Medication Nonpersistence Among Cohorts (N=926)

	Hazard Ratio	95% Hazard Ratio Confidence Interval		Wald X^2	p-value
Cohort					
AD/SGA	0.782	0.670	0.913	9.748	0.002*
Covariates					
Age	0.984	0.978	0.989	30.578	<0.001*
Female	1.052	0.899	1.231	0.402	0.526
African American	1.502	1.231	1.832	16.102	<0.001*
Hispanic	1.307	1.066	1.602	6.641	0.010*
Other[a]	1.244	0.808	1.914	0.983	0.321
Urban Residence	1.157	0.953	1.404	2.159	0.142
Charlson Comorbidity Index	1.018	0.962	1.077	0.377	0.539
Tobacco Use/Dependence	1.270	1.058	1.524	6.575	0.010*

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown
*Significant at p<0.05

Table 3.14: Secondary Analysis—Cox Proportional Hazards Regression Model Comparing Survival Time (Persistence Using a 60-Day Gap) Prior to Antidepressant Medication Nonpersistence Among Cohorts (N=926)

	Hazard Ratio	95% Hazard Ratio Confidence Interval		Wald X^2	p-value
Cohort					
AD/SGA	0.716	0.611	0.840	16.937	<0.001*
Covariates					
Age	0.979	0.974	0.985	46.090	<0.001*
Female	1.002	0.852	1.178	0.000	0.983
African American	1.506	1.226	1.851	15.220	<0.001*
Hispanic	1.312	1.064	1.618	6.451	0.011*
Other[a]	1.235	0.794	1.920	0.878	0.349
Urban Residence	1.227	1.004	1.499	3.995	0.046*
Charlson Comorbidity Index	1.023	0.968	1.083	0.653	0.419
Tobacco Use/Dependence	1.183	0.977	1.431	2.967	0.085

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown
*Significant at p<0.05

V. Objective 5: Suicide Ideation and Suicide Attempts

The purpose of Objective 5 was to determine if the rates of post-index suicide ideation and suicide attempts differ between patients in the AD and AD/SGA cohorts, while controlling for covariates. Due to the small sample sizes (i.e., 38 patients with suicide ideation and 9 patients with at least one suicide attempt), the dependent variables were aggregated. Therefore, one logistic regression analysis was employed, and the newly aggregated dependent variable—post-index suicide ideation and/or suicide attempt (1=yes; 0=no)—was tested. The primary independent variable being assessed was the study cohort (AD vs. AD/SGA). The study covariates utilized in both models included: age, gender, race/ethnicity, urban residence, Charlson Comorbidity Index score, and antidepressant persistence based on a 45-day permissible gap. Collinearity statistics showed that tolerance values ranged from 0.562 to 0.953 and variance inflation factor values (calculated as the inverse of tolerance) ranged from 1.050 to 1.780. Therefore, multicollinearity was not a statistical issue of concern. Table 3.15 provides descriptions and comparisons of the post-index suicide ideation and attempt rates between cohorts.

Approximately, 4.4% of the final sample had suicide ideation and/or a suicide attempt post-index (32 patients had suicide ideation only, 3 had attempted suicide, and 6 had both suicide ideation and at least one suicide attempt). A Hosmer and Lemeshow Goodness of Fit test yielded a non-significant p-value indicating good model fit with the data (χ^2=3.939; df=8; p=0.863). Table 3.16 displays the results of the logistic regression analysis assessing the likelihood of having suicide ideation and/or a suicide attempt. A chi-square test comparing the full model (i.e., model includes all covariates) to the constant model (i.e., model contains no covariates) was significant (χ^2=38.765; df=10; p<0.001), indicating that at least one covariate was related to the

outcome. The odds of having suicide ideation and/or a suicide attempt post-index was not significantly different between cohorts (OR=0.661; 95% CI=0.316-1.386; p=0.273), while controlling for other variables in the model. Compared to Caucasian patients, the likelihood of having suicide ideation and/or an attempt post-index was significantly lower by approximately 63.8% in African American patients (OR=0.362; 95% CI=0.137-0.957; p=0.040). Tobacco users/dependents were four times more likely to have post-index suicide ideation and/or a suicide attempt compared to non-users/dependents (OR=4.096; 95% CI=2.062-8.137; p<0.001). As patients persisted one day longer on their antidepressant therapy, the odds of having suicide ideation and/or a suicide attempt significantly decreased by 0.4% (OR=0.996; 95% CI=0.993-0.999; p=0.022). However, the other covariates (age, gender, being of Hispanic ethnicity, being of other race, urban residence, and Charlson Comorbidity Index score) were not significantly related to having suicide ideation and/or a suicide attempt post-index.

H_{05A}: The likelihood of having post-index suicide ideation and/or a suicide attempt does not differ between the AD and AD/SGA cohorts, while controlling for covariates.

[Not Rejected]

Table 3.15: Description and Comparison of Post-Index Suicide Ideation and Suicide Attempts Among Cohorts (N=926)

	AD (N=510)	AD/SGA (N=416)	p-value
Suicide Ideation (%)[a]			
Yes	5.3	2.6	0.043*
Suicide Attempt (%)[a]			
Yes	1.4	0.5	0.169
Suicide Ideation and/or Attempt (%)[a]			
Yes	5.3	2.6	0.043*

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Pearson's chi-square
*Significant at p<0.05

Table 3.16: Logistic Regression Analysis Comparing the Likelihood of Having Post-Index Suicide Ideation and/or a Suicide Attempt Among Cohorts (N=926)

	Odds Ratio	95% Confidence Interval		Wald X^2	p-value
Cohort					
AD/SGA	0.661	0.316	1.386	1.199	0.273
Covariates					
Age	0.985	0.959	1.011	1.264	0.261
Female	1.395	0.648	3.004	0.724	0.395
African American	0.362	0.137	0.957	4.199	0.040*
Hispanic	1.144	0.505	2.590	0.105	0.746
Other[a]	0.884	0.103	7.584	0.013	0.911
Urban Residence	0.981	0.420	2.292	0.002	0.965
Charlson Comorbidity Index	1.187	0.971	1.452	2.800	0.094
Tobacco Use/Dependence	4.096	2.062	8.137	16.207	<0.001*
Antidepressant Persistence[b]	0.996	0.993	0.999	5.215	0.022*

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown
[b]Persistence based on a 45-day permissible gap
*Significant at p<0.05

VI. Objective 6: Rates of Health Care Utilization

The purpose of Objective 6 was to identify if post-index health care utilization rates (psychotic depression-related hospitalizations, length of psychotic depression-related hospitalization stay, psychotic depression-related outpatient/emergency department visits, all-cause hospitalizations, length of all-cause hospitalization stay, all-cause outpatient/emergency department visits) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates. Approximately, 4.3% had at least one psychotic depression-related hospitalization post-index (36 patients had one hospitalization and 4 had two hospitalizations). Of these patients, the mean (±SD) length of stay for a psychotic depression-related hospitalization was 7.3 (±3.8) days. Due to the small sample sizes, the hypotheses testing psychotic depression-related hospitalizations and associated lengths of stay could not be tested.

Prior to running the statistical models, normality was checked using the Kolmogorov-Smirnov test. The tests indicated non-normality as the assumption of normality was rejected based on significant results ($p<0.001$). All models had a significant Likelihood Ratio chi-square test of alpha=0 ($p<0.001$), which indicated overdispersion (i.e., mean < variance) and that the data were better estimated using negative binomial regression models versus Poisson regression models. A significant Vuong test found that all-cause hospitalizations were better estimated using a zero-inflated negative binomial regression model rather than an ordinary negative binomial regression model ($p=0.004$). Therefore, four generalized linear regression models were employed (two negative binomial regression analyses, one negative binomial-logit hurdle regression analysis, and one zero-inflated negative binomial regression analysis). The dependent variables were psychotic depression-related outpatient/emergency department visits, all-cause hospitalizations, all-cause hospitalizations days (lengths of stay), and all-cause

outpatient/emergency department visits. The primary independent variable was the study cohort (AD vs. AD/SGA), and the study covariates were age, gender, race/ethnicity, urban residence, Charlson Comorbidity Index score, tobacco use and/or dependence, and antidepressant persistence based on a 45-day permissible gap. Table 3.17 provides descriptions and comparisons of the post-index health care utilization rates between cohorts.

Table 3.17: Description and Comparison of Post-Index Health Care Utilization Rates Among Cohorts (N=926)

	AD (N=510)	AD/SGA (N=416)	p-value
Psychotic Depression-Related Hospitalizations			
Mode	0	0	
Median	0	0	
Mean (±SD)[a]	0.04 (±0.2)	0.1 (±0.3)	0.968
Length of Psychotic Depression-Related Hospitalization Stay			
Mode	0	0	
Median	0	0	
Mean (±SD)[a]	0.3 (±1.3)	0.4 (±2.0)	0.956
Psychotic Depression-Related Outpatient/Emergency Department Visits			
Mode	1	1	
Median	2	4	
Mean (±SD)[a]	3.8 (±6.0)	6.6 (±8.2)	<0.001*
All-Cause Hospitalizations			
Mode	0	0	
Median	0	0	
Mean (±SD)[a]	0.4 (±0.8)	0.3 (±0.7)	<0.001*
Length of All-Cause Hospitalization Stay			
Mode	0	0	
Median	0	0	
Mean (±SD)[a]	2.4 (±5.9)	1.8 (±6.5)	<0.001*
All-Cause Outpatient/Emergency Department Visits			
Mode	15	8	
Median	18	17	
Mean (±SD)[a]	22.5 (±18.0)	21.4 (±18.5)	0.187

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Mann-Whitney U
*Significant at $p<0.05$

The mean (±SD) psychotic depression-related outpatient/emergency department visits, all-cause hospitalizations, all-cause hospitalizations days, and all-cause outpatient/emergency department visits were 5.1 (±7.2) visits, 0.3 (±0.8) hospitalizations, 2.1 (±6.2) days, and 22.0 (±18.2) visits, respectively. Tables 3.18-3.21 display the results of the generalized linear regression models using negative binomial regression, zero-inflated negative binomial regression, and negative binomial-logit hurdle regression. For each model, the Likelihood Ratio chi-square test was significant ($p<0.001$), indicating the rejection of the null hypothesis that all coefficients are equal to zero.

For total psychotic depression-related outpatient/emergency department visits, the AD/SGA cohort had significantly more visits (by approximately 60.0%) than the AD cohort (IRR=1.600; 95% CI=1.377-1.859; $p<0.001$), while controlling for other variables in the model. All covariates (except age, being African American, and tobacco use and/or dependence) remained significant predictors at $p<0.05$. Regarding total all-cause hospitalizations, although a univariate analysis found a significantly lower number of total all-cause hospitalizations for the combination cohort, multivariate analyses using zero-inflated negative binomial regression showed no significant difference between cohorts with race/ethnicity, Charlson Comorbidity Index, and antidepressant persistence being the only significant predictors of total all-cause hospitalizations ($p<0.05$). For patients with summated hospital lengths of stay greater than zero days, the AD/SGA cohort had significantly longer stays by approximately 42.3% than the AD cohort (IRR=1.423; 95% CI=1.072-1.888; $p=0.015$), while controlling for other variables in the model. Also, race/ethnicity, Charlson Comorbidity Index score, and antidepressant persistence remained significant predictors at $p<0.05$. However, the likelihood of having an all-cause hospitalization stay of at least one day was significantly lower in the AD/SGA cohort compared

to the AD cohort (OR=0.693; 95% CI=0.488-0.983; p=0.040). In other words, patients in the AD/SGA cohort were significantly less likely to have an all-cause hospitalization, but when these patients did have at least one, their hospitalization lengths of stay were significantly longer compared to the AD cohort. Finally, there was no significant difference between cohorts regarding total all-cause outpatient/emergency department visits; however, age, being of African American race, Charlson Comorbidity Index score, tobacco use and/or dependence, and antidepressant persistence were significant predictors ($p<0.05$).

H_{06A}: The number of post-index psychotic depression-related hospitalizations does not differ between the AD and AD/SGA cohorts, while controlling for covariates.

[Unable to Test]

H_{06B}: The number of post-index psychotic depression-related hospitalization days (sum of hospital says, in days) does not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Unable to Test]**

H_{06C}: The number of post-index psychotic depression-related outpatient/emergency department visits does not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Rejected]**

H_{06D}: The number of post-index all-cause hospitalizations does not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Not Rejected]**

H_{06E}: The number of post-index all-cause hospitalization days (sum of hospital stays in days) does not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Rejected]**

H_{06F}: The number of post-index all-cause outpatient/emergency department visits does not differ between the AD and AD/SGA cohorts, while controlling for covariates.

[Not Rejected]

Table 3.18: Negative Binomial Regression Analysis Comparing Psychotic Depression Outpatient/Emergency Department Visits Among Cohorts (N=926)

	IRR	95% Confidence Interval		Z-score	p-value
Cohort					
AD/SGA	1.600	1.377	1.859	6.13	<0.001*
Covariates					
Age	1.003	0.997	1.010	1.13	0.260
Female	0.726	0.621	0.847	-4.05	<0.001*
African American	1.104	0.908	1.343	0.99	0.321
Hispanic	1.274	1.043	1.556	2.37	0.018*
Other[a]	1.698	1.114	2.589	2.46	0.014*
Urban Residence	0.723	0.597	0.874	-3.35	<0.001*
Charlson Comorbidity Index	0.851	0.800	0.905	-5.14	<0.001*
Tobacco Use/Dependence	0.962	0.797	1.162	-0.40	0.690
Antidepressant Persistence[b]	1.002	1.001	1.003	7.09	<0.001*

IRR = incidence rate ratio; **AD** = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown;
[b]Persistence based on a 45-day permissible gap;
*Significant at $p<0.05$

Table 3.19: Zero-Inflated Negative Binomial Regression Analysis Comparing All-Cause Hospitalization Among Cohorts (N=926)

	IRR	95% Confidence Interval		Z-score	p-value
Count					
Cohort					
AD/SGA	1.376	0.933	2.030	1.61	0.107
Covariates					
Age	1.007	0.994	1.019	1.00	0.316
Female	1.361	0.946	0 .957	1.66	0.097
African American	0.430	0.272	0.679	-3.61	<0.001*
Hispanic	0.599	0.397	0.903	-2.45	0.014*
Other[a]	0.127	0.023	0.693	-2.38	0.017*
Urban Residence	0.847	0.562	1.278	-0.79	0.430
Charlson Comorbidity Index	1.206	1.088	1.337	3.57	<0.001*
Tobacco Use/Dependence	1.225	0.841	1.783	1.06	0.291
Antidepressant Persistence[b]	0.997	0.996	0.999	-3.73	<0.001*
Inflate					
Cohort					
AD/SGA	2.5981	0.953	4.244	3.09	0.002*
Covariates					
Age	0.0727	0.021	0.124	2.77	0.006*
Female	0.7076	-0.892	2.307	0.87	0.386
African American	-0.9280	-2.923	1.067	-0.91	0.362
Hispanic	-1.7406	-3.630	0.149	-1.81	0.071
Other[a]	-1.6571	-6.917	3.603	-0.62	0.537
Urban Residence	0.7145	-1.188	2.617	0.74	0.462
Charlson Comorbidity Index	-2.0498	-3.663	-0.437	-2.49	0.013*
Tobacco Use/Dependence	-1.7927	-3.503	-0.082	-2.05	0.040*
Antidepressant Persistence[b]	-0.0059	-0.012	0.000	-1.94	0.052

IRR = incidence rate ratio; **AD** = antidepressant; **SGA** = second-generation antipsychotic

[a]Other includes: Asian, Unknown;

[b]Persistence based on a 45-day permissible gap;

*Significant at $p<0.05$

Table 3.20: Negative Binomial-Logit Hurdle Model Regression Analysis Comparing All-Cause Hospitalization Days Among Cohorts (N=926)

	Ratio	95% Confidence Interval		Z-score	p-value
Logit					
Cohort					
AD/SGA	0.693[c]	0.488	0.983	-2.06	0.040*
Covariates					
Age	0.990[c]	0.976	1.003	-1.51	0.131
Female	1.351[c]	0.935	1.951	1.60	0.109
African American	0.471[c]	0.303	0.733	-3.33	0.001*
Hispanic	0.951[c]	0.624	1.448	-0.24	0.814
Other[a]	0.231[c]	0.051	1.054	-1.89	0.058
Urban Residence	0.642[c]	0.428	0.964	-1.89	0.033*
Charlson Comorbidity Index	1.420[c]	1.259	1.601	5.72	<0.001*
Tobacco Use/Dependence	1.473[c]	0.987	2.199	1.89	0.058
Antidepressant Persistence[b]	0.999[c]	0.997	1.000	-1.83	0.067
Zero-Truncated Negative Binomial					
Cohort					
AD/SGA	1.423[d]	1.072	1.888	2.44	0.015*
Covariates					
Age	1.011[d]	1.001	1.021	2.07	0.039*
Female	0.769[d]	0.576	1.027	-1.78	0.075
African American	0.707[d]	0.500	0.998	-1.97	0.049*
Hispanic	0.736[d]	0.531	1.021	-1.84	0.066
Other[a]	0.161[d]	0.036	0.725	-2.38	0.017*
Urban Residence	0.932[d]	0.679	1.279	-0.43	0.664
Charlson Comorbidity Index	1.111[d]	1.022	1.207	2.47	0.013*
Tobacco Use/Dependence	1.196[d]	0.881	1.623	1.15	0.251
Antidepressant Persistence[b]	0.999[d]	0.998	1.000	-1.48	0.138

AD = antidepressant; **SGA** = second-generation antipsychotic

[a]Other includes: Asian, Unknown;

[b]Persistence based on a 45-day permissible gap;

[c]Represents an odds ratio

[d]Represents an incidence rate ratio

*Significant at $p<0.05$

Table 3.21: Negative Binomial Regression Analysis Comparing All-Cause Outpatient/Emergency Department Visits Among Cohorts (N=926)

	IRR	95% Confidence Interval		Z-score	p-value
Cohort					
AD/SGA	1.005	0.914	1.106	0.11	0.912
Covariates					
Age	1.004	1.000	1.007	1.98	0.048*
Female	0.988	0.896	1.089	-0.25	0.803
African American	0.806	0.714	0.910	-3.49	<0.001*
Hispanic	1.058	0.935	1.198	0.89	0.373
Other[a]	0.920	0.702	1.204	-0.61	0.542
Urban Residence	1.016	0.901	1.146	0.26	0.794
Charlson Comorbidity Index	1.173	1.128	1.220	8.01	<0.001*
Tobacco Use/Dependence	1.285	1.145	1.442	4.26	<0.001*
Antidepressant Persistence[b]	1.001	1.001	1.001	5.59	<0.001*

IRR = incidence rate ratio; **AD** = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown;
[b]Persistence based on a 45-day permissible gap;
*Significant at $p<0.05$

VII. Objective 7: Costs of Health Care Utilization

The purpose of Objective 7 was to determine if post-index adjusted health care costs (psychotic depression-related medication, psychotic depression-related medical, psychotic depression-related total, all-cause medication, all-cause medical, and all-cause total costs) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates. Due to the distribution of the dependent variables, six generalized linear regression models with gamma distributions and log-link functions were employed with the dependent variables being psychotic depression-related medication costs, psychotic depression-related medical costs, psychotic depression-related total costs, all-cause medication costs, all-cause medical costs, and all-cause total costs. The primary independent variable assessed was the study cohort (AD vs. AD/SGA). The study covariates utilized in the models included: age, gender, race/ethnicity, urban residence, Charlson Comorbidity Index score, and antidepressant persistence based on a 45-day permissible gap. For psychotic depression-related medical costs, a two-part model for continuous outcomes (a logit model and a generalized linear model with a gamma distribution and log-link function) was utilized due to the large frequency of $0 dollars.

Prior to running the generalized linear models with gamma distributions and log-link functions, normality was checked using the Kolmogorov-Smirnov test. The tests indicated non-normality, where the assumption of normality was rejected based on significant results ($p<0.001$). For each model, a Likelihood Ratio chi-square test comparing the full models (i.e., model includes all covariates) to the constant model (i.e., model contains no covariates) was significant ($p<0.001$), indicating that at least one covariate was related to the outcome. Table 3.22 provides descriptions and comparisons of the post-index health care costs between cohorts.

Table 3.22: Description and Comparison of Post-Index Health Care Costs Among Cohorts (N=926)

	AD (N=510)	AD/SGA (N=416)	p-value
Psychotic Depression-Related Medication Costs Mean (±SD)[a]	$537.87 (±752.37)	$3163.74 (±3128.82)	<0.001*
Psychotic Depression-Related Medical Costs Mean (±SD)[a]	$712.80 (±2217.29)	$1250.57 (±3107.19)	<0.001*
Psychotic Depression-Related Total Costs Mean (±SD)[a]	$1250.67 (±2501.68)	$4414.30 (±4594.32)	<0.001*
All-Cause Medication Costs Mean (±SD)[a]	$2741.10 (±6026.81)	$4463.19 (±5199.85)	<0.001*
All-Cause Medical Costs Mean (±SD)[a]	$19283.47 (±40209.56)	$15896.56 (±30795.41)	0.028*
All-Cause Total Costs Mean (±SD)[a]	$22024.57 (±41237.86)	$20359.74 (±31552.52)	0.293

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Generalized linear model univariate analysis with gamma distribution and log-link function
*Significant at p<0.05

For psychotic depression-related medication costs, the mean (±SD) total adjusted costs were $1,717.53 (±2,532.07). Table 3.23 displays the results of the generalized linear regression analysis. The AD/SGA cohort psychotic depression-related medication costs were almost six times significantly higher than the AD cohort [Exp(B)=5.982; 95% CI=5.221-6.854; p<0.001], while controlling for other variables in the model. Age, place of residence, and antidepressant persistence were also significant predictors of psychotic depression-related medication costs (p<0.05).

For psychotic depression-related medical costs, the mean (±SD) adjusted costs were $954.39 (±2,666.17), where 15.6% of the final sample had $0 accrued costs. Table 3.24 displays the results of the two-part model regression analysis using a logit model and a generalized linear regression model. Results show that the AD/SGA cohort had over a two times significantly higher likelihood of having psychotic depression-related medical costs that were greater than $0, compared to the AD cohort (OR=2.691; 95% CI=1.755-4.127; p<0.001). Of those patients with psychotic depression-related medical costs greater than $0, costs were 51.0% higher for the AD/SGA cohort versus the AD cohort [Exp(B)=1.510; 95% CI=1.235-1.845; p<0.001]. Gender, being of Hispanic ethnicity, being of other race, and antidepressant persistence were significant predictors of psychotic depression-related medical costs greater than $0 (p<0.05).

For the psychotic depression-related total costs, the mean (±SD) total adjusted costs were $2671.91 (±3,923.37). Table 3.25 displays the results of the generalized linear regression analysis. Results showed that the AD/SGA cohort had over three times significantly higher costs than the AD cohort [Exp(B)=3.413; 95% CI=2.938-3.965; p<0.001], while controlling for other variables in the model. Gender, being of other race, and antidepressant persistence remained significant predictors at p<0.05.

For all-cause medication costs, the mean (±SD) total adjusted costs were $3,514.74 (±5,731.71). Table 3.26 displays the results of the generalized linear regression analysis. All-cause medication costs were significantly higher by 79.1% for the AD/SGA cohort, compared to the AD cohort [Exp(B)=1.791; 95% CI=1.558-2.060; p<0.001], while controlling for other variables in the model. Age, gender, being African American, being of other race, Charlson Comorbidity Index score, and antidepressant persistence were significant predictors of all-cause medication costs (p<0.05).

For all-cause medical costs, the mean (±SD) total adjusted costs were $17,761.92 (±36,304.30). Table 3.27 displays the results of the generalized linear regression analysis. There was no significant difference between cohorts; however, all independent variables (except being of other race and antidepressant persistence) remained significant predictors at p<0.05.

Finally for all-cause total adjusted costs, the mean (±SD) total adjusted costs were $21,276.65 (±37,190.22). Table 3.28 displays the results of the generalized linear regression analysis. The significance results for all-cause total costs were similar to the results for all-cause medical costs.

H_{07A}: The post-index psychotic depression-related medication costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Rejected]**

H_{07B}: The post-index psychotic depression-related medical costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Rejected]**

H_{07C}: The post-index psychotic depression-related total costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Rejected]**

H_{07D}: The post-index all-cause medication costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Rejected]**

H_{07E}: The post-index all-cause medical costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Not Rejected]**

H_{07F}: The post-index all-cause total costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Not Rejected]**

Table 3.23: Generalized Linear Model Regression Analysis Comparing Psychotic Depression-Related Medication Costs Among Cohorts (N=926)

	Exp(B)	95% Confidence Interval Exp(B)		Wald X^2	p-value
Cohort					
AD/SGA	5.982	5.221	6.854	664.219	<0.001*
Covariates					
Age	1.006	1.001	1.012	4.797	0.029*
Female	1.031	0.895	1.187	0.179	0.672
African American	0.850	0.712	1.016	3.188	0.074
Hispanic	1.069	0.891	1.284	0.516	0.472
Other[a]	1.107	0.747	1.641	0.257	0.612
Urban Residence	0.804	0.674	0.959	5.913	0.015*
Charlson Comorbidity Index	0.965	0.920	1.013	2.071	0.150
Tobacco Use/Dependence	0.946	0.799	1.119	0.419	0.517
Antidepressant Persistence[b]	1.004	1.004	1.005	240.148	<0.001*

AD = antidepressant; **SGA** = second-generation antipsychotic

[a]Other includes: Asian, Unknown

[b]Persistence based on a 45-day permissible gap

*Significant at $p<0.05$

Table 3.24: Two-Part Model Regression Analysis Comparing Psychotic Depression-Related Medical Costs Among Cohorts (N=926)

	Exp(B)	95% Confidence Interval		Wald X^2	p-value
Logit					
Cohort					
AD/SGA	2.691	1.755	4.127	20.594	<0.001*
Covariates					
Age	0.998	0.983	1.014	0.055	0.815
Female	0.987	0.656	1.486	0.004	0.950
African American	1.308	0.795	2.152	1.117	0.291
Hispanic	1.153	0.707	1.879	0.325	0.569
Other[a]	1.686	0.463	6.133	0.628	0.428
Urban Residence	0.840	0.515	1.371	0.486	0.486
Charlson Comorbidity Index	0.748	0.664	0.843	22.888	<0.001*
Tobacco Use/Dependence	1.432	0.873	2.348	2.022	0.155
Antidepressant Persistence[b]	1.002	1.000	1.003	5.019	0.025*
Generalized Linear Model[c]					
Cohort					
AD/SGA	1.510	1.235	1.845	16.173	<0.001*
Covariates					
Age	0.995	0.987	1.003	1.671	0.196
Female	0.620	0.503	0.763	20.269	<0.001*
African American	0.939	0.718	1.228	.213	0.644
Hispanic	1.458	1.111	1.914	7.392	0.007*
Other[a]	2.941	1.651	5.238	13.417	<0.001*
Urban Residence	1.134	0.870	1.478	.869	0.351
Charlson Comorbidity Index	1.051	0.960	1.151	1.145	0.285
Tobacco Use/Dependence	1.244	0.971	1.594	2.993	0.084
Antidepressant Persistence[b]	1.002	1.001	1.002	15.771	<0.001*

OR = odds ratio; **AD** = antidepressant; **SGA** = second-generation antipsychotic

[a]Other includes: Asian, Unknown

[b]Persistence based on a 45-day permissible gap

[c]Gamma distribution and log-link function

*Significant at $p<0.05$

Table 3.25: Generalized Linear Model Regression Analysis Comparing Psychotic Depression-Related Total Costs Among Cohorts (N=926)

	Exp(B)	95% Confidence Interval Exp(B)		Wald X^2	p-value
Cohort					
AD/SGA	3.413	2.938	3.965	257.679	<0.001*
Covariates					
Age	1.000	0.994	1.006	0.000	0.991
Female	0.827	0.709	0.965	5.807	0.016*
African American	0.865	0.711	1.051	2.123	0.145
Hispanic	1.196	0.980	1.461	3.099	0.078
Other[a]	1.710	1.105	2.645	5.810	0.016*
Urban Residence	0.924	0.762	1.121	0.639	0.424
Charlson Comorbidity Index	0.969	0.916	1.025	1.218	0.270
Tobacco Use/Dependence	1.126	0.936	1.353	1.584	0.208
Antidepressant Persistence[b]	1.003	1.003	1.004	117.537	<0.001*

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown
[b]Persistence based on a 45-day permissible gap
*Significant at p<0.05

Table 3.26: Generalized Linear Model Regression Analysis Comparing All-Cause Medication Costs Among Cohorts (N=926)

	Exp(B)	95% Confidence Interval Exp(B)		Wald X^2	p-value
Cohort					
AD/SGA	1.791	1.558	2.060	67.125	<0.001*
Covariates					
Age	1.015	1.010	1.021	32.000	<0.001*
Female	0.780	0.677	0.900	11.628	0.001*
African American	0.814	0.682	0.972	5.174	0.023*
Hispanic	0.872	0.724	1.050	2.096	0.148
Other[a]	2.297	1.534	3.439	16.310	<0.001*
Urban Residence	1.083	0.909	1.291	0.805	0.370
Charlson Comorbidity Index	1.222	1.155	1.293	48.330	<0.001*
Tobacco Use/Dependence	0.999	0.842	1.185	0.000	0.987
Antidepressant Persistence[b]	1.002	1.002	1.003	89.090	<0.001*

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown
[b]Persistence based on a 45-day permissible gap
*Significant at p<0.05

Table 3.27: Generalized Linear Model Regression Analysis Comparing All-Cause Medical Costs Among Cohorts (N=926)

	Exp(B)	95% Confidence Interval Exp(B)		Wald X^2	p-value
Cohort					
AD/SGA	0.964	0.810	1.146	0.173	0.677
Covariates					
Age	1.011	1.005	1.018	11.167	0.001*
Female	1.397	1.172	1.666	13.923	<0.001*
African American	0.718	0.575	0.895	8.654	0.003*
Hispanic	0.752	0.602	0.939	6.312	0.012*
Other[a]	0.755	0.467	1.220	1.321	0.250
Urban Residence	1.291	1.040	1.601	5.385	0.020*
Charlson Comorbidity Index	1.342	1.248	1.444	62.557	<0.001*
Tobacco Use/Dependence	1.907	1.553	2.341	38.021	<0.001*
Antidepressant Persistence[b]	1.000	0.999	1.001	0.136	0.713

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown
[b]Persistence based on a 45-day permissible gap
*Significant at p<0.05

Table 3.28: Generalized Linear Model Regression Analysis Comparing All-Cause Total Costs Among Cohorts (N=926)

	Exp(B)	95% Confidence Interval Exp(B)		Wald X^2	p-value
Cohort					
AD/SGA	1.081	0.936	1.248	1.125	0.289
Covariates					
Age	1.011	1.005	1.016	15.506	<0.001*
Female	1.255	1.085	1.452	9.325	0.002*
African American	0.730	0.608	0.877	11.322	0.001*
Hispanic	0.772	0.641	0.929	7.473	0.006*
Other[a]	0.884	0.592	1.318	0.367	0.544
Urban Residence	1.248	1.043	1.492	5.876	0.015*
Charlson Comorbidity Index	1.314	1.238	1.396	79.664	<0.001*
Tobacco Use/Dependence	1.760	1.483	2.089	41.961	<0.001*
Antidepressant Persistence[b]	1.000	1.000	1.001	2.119	0.146

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown
[b]Persistence based on a 45-day permissible gap
*Significant at p<0.05

VIII. Objective 8: Dyslipidemia and Diabetes Mellitus Risks of Medication Therapy

The purpose of Objective 8 was to determine if the risks of medication therapy (incident dyslipidemia, incident diabetes mellitus, and incident extrapyramidal symptoms) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates. Since a total of 12 patients were diagnosed with extrapyramidal symptoms post-index, only two Cox proportional hazards regression models were employed with the continuous dependent variables being progression time to the first diagnosis of dyslipidemia and progression time to the first diagnosis of diabetes mellitus. The primary independent variable was the study cohort (AD vs. AD/SGA), and the study covariates were age, gender, race/ethnicity, urban residence, Charlson Comorbidity Index score, tobacco use and/or dependence, and antidepressant persistence using a 45-day gap. For the dyslipidemia analysis, patients were censored if they did not have a diagnosis for dyslipidemia through day 365 of the post-index period. For the diabetes mellitus analysis, patients were censored if they did not have a diagnosis for diabetes mellitus through day 365 of the post-index period.

Prior to utilizing statistical analyses, multicollinearity was assessed using collinearity statistics and was found to be absent based on the tolerance and variance inflation factor scores. The proportionality of hazards assumption was met for the dyslipidemia analysis (Wald χ^2=12.314, df=10, p=0.265). However, the proportionality of hazards assumption was not met for the diabetes mellitus analysis (Wald χ^2=18.682, df=10, p=0.045), where a significant gender-time interaction was identified (p=0.008). Since treatment cohorts were established at index and suppressing this interaction would estimate an average effect over the observed range of time for the data,[2] the regression model without the interaction could be retained. Nevertheless, a sensitivity analysis using the gender-time interaction was used to assess whether significant

changes in the cohort variable occurred. Descriptions and comparisons of the rates of incident dyslipidemia, diabetes mellitus, and extrapyramidal symptoms are provided in Tables 3.6 and 3.7.

For the 134 patients who had at least one diagnosis for dyslipidemia, the mean time (±SD) to dyslipidemia progression was 181.9 days (±96.4). For the AD cohort, the mean time (±SD) to dyslipidemia progression was 171.9 (±93.5), and for the AD/SGA cohort, the mean time (±SD) was 196.1 (±99.5). Table 3.29 provides the results for the Cox proportional hazards regression model comparing time to progression for dyslipidemia between cohorts. The global null hypothesis test was significant (χ^2=52.832; df=10; p<0.001), indicating the rejection of the null hypothesis that all coefficients are equal to zero. Results showed that there was no significant difference in time to progression (survival time) among cohorts, while controlling for other covariates in the model. However, as age increased by one year, the hazard of progression to dyslipidemia significantly increased by approximately 4.1% (HR=1.041; 95% CI=1.025-1.057; p<0.001). Compared to non-tobacco users/dependents, the hazards of medication nonpersistence was significantly higher by 66.8% for tobacco users/dependents (HR=1.668; 95% CI=1.137-2.446; p=0.009). The remaining covariates were not significantly related to the dependent variable.

For the 49 patients who had at least one diagnosis for diabetes mellitus, the mean time (±SD) to diabetes mellitus was 169.5 days (±92.6). For the AD cohort, the mean time (±SD) to diabetes mellitus progression was 151.1 (±79.2), and for the AD/SGA cohort, the mean time (±SD) was 192.0 (±104.3). Table 3.30 provides the results for the Cox proportional hazards regression model comparing time to progression for diabetes mellitus between cohorts. The global null hypothesis test was significant (χ^2=29.401; df=10; p=0.001), indicating the rejection

of the null hypothesis that all coefficients are equal to zero. Similarly to dyslipidemia, results showed that there was no significant difference in time to progression to diabetes mellitus (survival time) among cohorts, while controlling for other covariates in the model. Also, as age increased by one year, the hazard of progression to diabetes mellitus significantly increased by about 3.5% (HR=1.035; 95% CI=1.009-1.061; p=0.007). Interestingly, the hazards of progression to diabetes mellitus were significantly higher—more than twice as high—in Hispanic patients compared to Caucasian patients (HR=2.261; 95% CI=1.018-5.023; p=0.045). Lastly, as antidepressant persistence increased by one day, the hazards of the progression to diabetes mellitus significantly increase by 0.3% (HR=1.003; 95% CI=1.001-1.005; p=0.008). The remaining covariates were not significantly related to the dependent variable. A sensitivity analysis using the covariates listed above, as well as the gender-time interaction, found no significant difference between cohorts (HR=0.815; 95% CI=0.449-1.477; p=0.500).

H_{08A}: The progression to the first diagnosis of dyslipidemia (after a 45-day post-index period) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.

[Not Rejected]

H_{08B}: The progression to the first diagnosis of diabetes mellitus (after a 45-day post-index period) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.

[Not Rejected]

H_{08C}: The progression to the first diagnosis of extrapyramidal symptoms post-index does not differ between the AD and AD/SGA cohorts, while controlling for covariates. **[Unable to Test]**

Table 3.29: Cox Proportional Hazards Regression Model Comparing Dyslipidemia Time to Progression Among Cohorts (N=709)

	Hazard Ratio	95% Hazard Ratio Confidence Interval		Wald X^2	p-value
Cohort					
AD/SGA	0.750	0.523	1.076	2.435	0.119
Covariates					
Age	1.041	1.025	1.057	27.191	<0.001*
Female	1.030	0.710	1.495	0.025	0.875
African American	0.791	0.499	1.254	0.993	0.319
Hispanic	1.222	0.784	1.906	0.785	0.376
Other[a]	1.384	0.574	3.338	0.522	0.470
Urban Residence	1.310	0.817	2.101	1.255	0.263
Charlson Comorbidity Index	1.026	0.887	1.187	0.123	0.725
Tobacco Use/Dependence	1.668	1.137	2.446	6.839	0.009*
Persistence (45-day gap)	1.000	0.999	1.002	0.083	0.773

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown
*Significant at p<0.05

Table 3.30: Cox Proportional Hazards Regression Model Comparing Diabetes Mellitus Time to Progression Among Cohorts (N=750)

	Hazard Ratio	95% Hazard Ratio Confidence Interval		Wald X^2	p-value
Cohort					
AD/SGA	0.822	0.453	1.490	0.419	0.517
Covariates					
Age	1.035	1.009	1.061	7.304	0.007*
Female	1.417	0.745	2.693	1.129	0.288
African American	1.320	0.582	2.997	0.442	0.506
Hispanic	2.261	1.018	5.023	4.012	0.045*
Other[a]	1.989	0.424	9.327	0.761	0.383
Urban Residence	0.963	0.446	2.082	0.009	0.924
Charlson Comorbidity Index	1.232	0.992	1.529	3.577	0.059
Tobacco Use/Dependence	1.417	0.730	2.750	1.059	0.303
Persistence (45-day gap)	1.003	1.001	1.005	7.054	0.008*

AD = antidepressant; **SGA** = second-generation antipsychotic
[a]Other includes: Asian, Unknown
*Significant at p<0.05

Table 3.31 displays the results of the hypotheses testing for the study.

Table 3.31: Results of Hypotheses Testing

Objectives/Hypotheses	Statistical Analysis	Result
Objective 1: To describe and compare the baseline socio-demographic and clinical characteristics of Texas Medicaid patients with MD-Psy who utilize either antidepressant monotherapy (AD cohort) or combination therapy with an antidepressant and a second-generation antipsychotic (AD/SGA cohort).	Descriptive Statistics	**No Hypothesis**
Objective 2: To describe and compare the post-index clinical characteristics of the AD and AD/SGA cohorts.	Descriptive Statistics	**No Hypothesis**
Objective 3: To determine if the rates of medication adherence (medication possession ratio – MPR and proportion of days covered – PDC) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.		
H_{03A}: The likelihood of being adherent as measured by MPR ≥ 80% to antidepressant therapy does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Logistic Regression	**Rejected**
H_{03B}: The likelihood of being adherent as measured by PDC ≥ 80% to antidepressant therapy does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Logistic Regression	**Rejected**
Objective 4: To determine if the risk of medication nonpersistence differs between patients in the AD and AD/SGA cohorts, while controlling for covariates.		
H_{04A}: The time, in days, to antidepressant medication nonpersistence (using a 45-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Cox Proportional Hazards Regression	**Rejected**

Table 3.31: Results of Hypotheses Testing (continued)

Objectives/Hypotheses	Statistical Analysis	Result
H_{04B}: The time, in days, to antidepressant medication nonpersistence (using a 30-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Cox Proportional Hazards Regression	**Rejected**
H_{04C}: The time, in days, to antidepressant medication nonpersistence (using a 60-day gap of no medication) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Cox Proportional Hazards Regression	**Rejected**
Objective 5: To determine if the rate of post-index suicide ideation and suicide attempts differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.		
H_{05A}: The likelihood of having post-index suicide ideation and/or suicide attempt does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Logistic Regression	**Not Rejected**
Objective 6: To identify if post-index health care utilization rates (psychotic depression-related hospitalizations, length of psychotic depression-related hospitalization stay, psychotic depression-related outpatient/emergency department visits, all-cause hospitalizations, length of all-cause hospitalization stay, all-cause outpatient/emergency department visits) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.		
H_{06A}: The number of post-index psychotic depression-related hospitalizations does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Descriptive Statistics	**Unable to Test**
H_{06B}: The number of post-index psychotic depression-related hospitalization days (sum of hospital says, in days) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Descriptive Statistics	**Unable to Test**

Table 3.31: Results of Hypotheses Testing (continued)

Objectives/Hypotheses	Statistical Analysis	Result
H_{06C}: The number of post-index psychotic depression-related outpatient/emergency department visits does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Negative Binomial Regression	**Rejected**
H_{06D}: The number of post-index all-cause hospitalizations does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Zero-Inflated Negative Binomial Regression	**Not Rejected**
H_{06E}: The number of post-index all-cause hospitalization days (sum of hospital stays, in days) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Zero-Truncated Negative Binomial Regression	**Rejected**
H_{06F}: The number of post-index all-cause outpatient/emergency department visits does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Negative Binomial Regression	**Not Rejected**
Objective 7: To determine if post-index adjusted health care costs (psychotic depression-related and all-cause medication, medical, and total costs) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.		
H_{07A}: The post-index psychotic depression-related medication costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	GLM with gamma distribution and log-link function	**Rejected**
H_{07B}: The post-index psychotic depression-related medical costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	GLM with gamma distribution and log-link function	**Rejected**
H_{07C}: The post-index psychotic depression-related total costs (psychotic depression-related prescription and psychotic depression-related medical costs) do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	GLM with gamma distribution and log-link function	**Rejected**

Table 3.31: Results of Hypotheses Testing (continued)

Objectives/Hypotheses	Statistical Analysis	Result
H_{07D}: The post-index all-cause medication costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	GLM with gamma distribution and log-link function	**Rejected**
H_{07E}: The post-index all-cause medical costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	GLM with gamma distribution and log-link function	**Not Rejected**
H_{07F}: The post-index all-cause total costs do not differ between the AD and AD/SGA cohorts, while controlling for covariates.	GLM with gamma distribution and log-link function	**Not Rejected**
Objective 8: To determine if the risks of medication therapy (incident dyslipidemia, incident diabetes mellitus, and incident extrapyramidal symptoms) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.		
H_{08A}: The progression to the first diagnosis of dyslipidemia (after a 45-day post-index period) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Cox Proportional Hazards Regression	**Not Rejected**
H_{08B}: The progression to the first diagnosis of diabetes mellitus (after a 45-day post-index period) does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Cox Proportional Hazards Regression	**Not Rejected**
H_{08C}: The progression to the first diagnosis of extrapyramidal symptoms post-index does not differ between the AD and AD/SGA cohorts, while controlling for covariates.	Descriptive Statistics	**Unable to Test**

AD = antidepressant; **SGA** = second-generation antipsychotic; **MPR**= medication possession ratio; **PDC** = proportion of days covered; **GLM** = generalized linear model

CHAPTER 3 BIBLIOGRAPHY

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Chapter 4: Discussion and Conclusion

CHAPTER OVERVIEW

This chapter provides a comprehensive discussion of the study results. The chapter begins by reintroducing the study purpose and objectives. It then provides detailed explanations and comparisons between related studies found in the literature. The chapter closes with an explanation of the study limitations, recommendations for future research, final conclusions, and implications.

REVIEW OF STUDY PURPOSE

The purpose of the present study was to assess the medication therapy of patients with unipolar psychotic depression in relation to medication adherence, medication persistence, suicide ideation and attempts, health care utilization, health care costs, and medication safety using Texas Medicaid data from September 2007 to December 2012. The present study aimed to enhance the understanding of this severe subtype of major depressive disorder and provide information to fill the gaps in knowledge that clinicians and decision-makers may use when considering treatment options for unipolar psychotic depression. To our knowledge, the present study is the first retrospective analysis utilizing a large database claims dataset to primarily assess unipolar major depressive disorder with psychotic features.

STUDY OBJECTIVES

The present study assessed eight objectives and eighteen hypotheses. For each objective, the results are evaluated and discussed, as well as compared and contrasted with related studies.

I. Objectives 1 and 2

The aim of Objective 1 was to describe and compare the baseline socio-demographic and clinical characteristics of patients with psychotic depression who utilize either antidepressant monotherapy (AD cohort) or combination therapy with an antidepressant plus a second-generation antipsychotic (AD/SGA cohort). The aim of Objective 2 was to assess post-index tobacco use and/or dependence among cohorts.

There still remains a lack of consensus among international guidelines in regards to the treatment of psychotic depression. In European countries, antidepressant monotherapy remains first-line therapy; while in the US, either combination therapy with an antidepressant plus an antipsychotic agent or electroconvulsive therapy is considered the best therapy.[1] Surprisingly, in the present study, more than half of the patients in our final sample utilized antidepressant monotherapy (AD cohort = 510 patients) versus combination therapy (AD/SGA cohort = 416 patients). This deviation from first-line recommendations could be explained by a number of reasons that the present study was unable to measure; however, it is important to acknowledge that it is recommended that providers weigh the risks and benefits of treatment when prescribing therapy. Present

comorbidities (e.g., diabetes mellitus and dyslipidemia) and the known adverse events of antipsychotics (e.g., increased risk of elevated blood glucose, lipids, and weight gain) could potentially influence prescribing habits favoring antidepressant monotherapy. This may be the case in the present study as the AD cohort had a slightly but significantly higher mean Charlson Comorbidity Index score, compared to the AD/SGA cohort (0.8 versus 0.5, $p<0.001$).

The overall age and percent of females in the present study is consistent with the literature focusing on first-admission or first-episode patients with psychotic depression.[2-4] However, in contrast to previous studies on psychotic depression, the majority of patients were of Caucasian race (studies ranged from 60.7% to 85.2%).[2,3,5-7] In the present study, the percent of Caucasians was much smaller at 25.2% as the majority of the final sample was of either African American race (34.9%) or Hispanic ethnicity (36.7%). (Caucasians represent approximately 19% of the total population of non-elderly Texas Medicaid patients.)[8] Since all of the patients in the present study were publically insured through the Texas Medicaid program (an indication of low socio-economic status), our sample may be different from much of the existing literature, where less than one-quarter of psychotically depressed patients either utilized public insurance or comprised the bottom socio-economic status quartile.[3,5] Due to these differences, the present study provides a unique addition to the present literature on psychotic depression, as there is a dearth of information regarding minority and indigent populations.

The present study also contributes by increasing the knowledge related to tobacco use and/or dependence and place of residence (urban versus rural) in psychotic

depression. While the percent of tobacco users and/or dependents was similar to the percent of lifetime smokers in a previous study on psychotic depression,[3] the present study offered more insight into the relationship between tobacco use and/or dependence and adherence, persistence, suicidality, heath care utilization, expenditures, and medication safety. Correspondingly, the analysis of urban versus rural residence has not been previously assessed in other psychotic depression studies, where the exploration of rural versus urban living could be of merit to payers, such as Texas Medicaid.

II. Objectives 2 through 4

The aim of Objective 2 was to describe the post-index AD persistence and SGA persistence using 45-day permissible gaps among cohorts. The aim of Objective 3 was to determine if the rates of antidepressant medication adherence (medication possession ratio – MPR and proportion of days covered – PDC) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates. The aim of Objective 4 was to determine if the risk of antidepressant medication nonpersistence differs between patients in the AD and AD/SGA cohorts, while controlling for covariates.

The present study reflects a novel approach to evaluating medication adherence in patients diagnosed with major depressive disorder with psychotic features. To date, this is the first known study analyzing treatment adherence in psychotically depressed patients using MPR and PDC. Overall, 38.3% and 33.0% of patients were adherent to their antidepressant medications based on MPR $\geq$ 80% and PDC $\geq$ 80%, respectively. In the literature, only one study was remotely similar in analyzing medication usage as a

percentage of time as calculated based on responses from face-to-face patient interviews. The results were similar to the present study, where the authors reported 39.1% and 31.4% of patients utilized their antidepressant medications "75% to 100%" of the time from discharge to six months and from six months to 24 months, respectively. Univariate analysis found that younger age was associated with a lower likelihood of regular medication use at 75% to 100% of the time, compared to older age.[2] Similarly, in the present study, increasing age was associated with higher likelihoods of antidepressant adherence for both MPR and PDC. Utilizing combination therapy, being Caucasian versus African American, and the absence of tobacco use and/or dependence were also associated with higher likelihoods of antidepressant adherence for MPR and PDC.

The present study is also innovative in its approach by analyzing medication persistence in relation to both second-generation antipsychotic medications and antidepressant medications. While there are no studies in the literature that assess medication persistence in psychotic depression, this analysis can be compared to the current recommendations for medication treatment continuation in psychotic depression.

Although four to nine months of antipsychotic use has been advocated; currently, there is little consensus in how long a patient with psychotic depression should be treated with an antipsychotic medication.[9] The Texas Medication Algorithm Project[10] recommends continuing an antipsychotic medication for one to two months during the continuation phase, where a psychotically depressed patient has achieved a clinical response but is not yet in remission. Wijkstra and associates[11] found that, after seven weeks of acute treatment, continued treatment with a second-generation antipsychotic

was effective and well-tolerated at the four month follow-up period in patients with psychotic depression. Antipsychotic-related recommendations and previous results in the literature are comparable to the results of the present study, where the mean use of second-generation antipsychotics was approximately 179 days (or almost six months) before a gap in therapy occurred.

In relation to antidepressant treatment, the recommendation for antidepressant treatment has ranged from six to nine months after the acute phase to at least one year after remission has been achieved.[10,12] Overall, patients in the present study persisted on their antidepressant medications for approximately 172 days (or about six months) before the occurrence of a gap in therapy—less than the recommended treatment time for psychotic depression. The risk of antidepressant nonpersistence was significantly higher in antidepressant monotherapy users, younger patients, minorities (African Americans and Hispanics), and those with tobacco use and/or dependence. The study results may be a consequence of many unmeasured factors, such as receiving second-line medication therapy, socio-demographic disadvantages, and having less investment in their overall health.

III. Objective 5

The aim of Objective 5 was to determine if the rates of post-index suicide ideation and suicide attempts differ between patients in the AD and AD/SGA cohorts, while controlling for covariates. Overall, the rates of suicide ideation and suicide attempts were low for both the 6-month pre-index period (suicide ideation = 4.1%; suicide attempts =

0.4%) and the 12-month post-index period (suicide ideation = 4.1%; suicide attempts = 1.0%).

Previous studies[5,6,13] assessing patients with psychotic depression report a lifetime history of suicide ideation and suicide attempts as high as 55.8% and 36.7%, respectively. A nine-month long hospital study in Milan reported a low rate of previous suicide attempts at 7.1% (n=4 of 18) in their sample of patients with psychotic depression, where the mean number of previous attempts was 0.39 (±0.85).[14] Compared to the above studies, the lower rates of suicide ideation and suicide attempts are reasonable in the present study due to the shorter pre-index period and the inability to obtain lifetime histories through patient interviews. In addition, the use of claims data to detect suicide ideation may underestimate its true rate, as it may be underreported. While completed suicide was not assessed in the present study, a nationwide Danish study found that 2.3% of patients with psychotic depression completed suicide over a nineteen-year period.[15] Future studies should explore the role of psychotic depression in completed suicides.

Comparatively, studies by Gaudiano and associates[6,16] reported higher rates of current suicide ideation (16.7%; n=10 of 60) and recent suicide attempts (10.0%; n=6 of 60) in patients with psychotic depression, and Schaffer and associates[13] estimated active suicidal ideation and current suicide attempts at 16.9% (n=31 of 183) and 20.8% (n=38 of 183), respectively, in the STOP-PD study. A Nigerian study[17] also found high rates of current suicide ideation (58.1%; n=75 of 129) and suicide attempts (17.8%; n=23 of 129) in patients with psychotic depression in sub-Saharan Africa. A four-year long cohort study found a very high first-hospital admission rate for suicide attempts at 36.8% (n=32

of 87). Dissimilar rates of suicidality between the present study and results found in the literature are most likely attributed to differences in study designs such as: comparing psychotic depressed patients versus non-psychotic depressed patients, the use of prospective versus retrospective designs, and the use of longer study periods. Conversely from other studies, Johnson and associates[5] reported zero new suicide attempts in their psychotic depressed group (N=92) one year after initial patient interviews.

In the present study, tobacco use and/or dependence and lower antidepressant medication persistence were significantly associated with a higher likelihood of suicidality (i.e., suicide ideation and attempts). These are reasonable findings as this may reflect suicidal patients' decreased propensity to take a more active role in their overall health due to their more detrimental mental health state. Only two psychotic depression-related studies have evaluated factors associated with suicidality.[13,15] Schaffer and associates[13] reported that male gender, Hispanic ethnicity, and higher depression scores were associated with severe intensity of current suicidality in patients with psychotic depression ($p<0.05$). The other study was a large nationwide, register-based study in Denmark found that older age, male gender, and previous self-harm were significant risk factors for completed suicide in patients with psychotic depression ($p<0.05$); however, receiving a disability pension was protective against suicide ($p<0.05$).[15] Comparatively, the lack of the present study's ability to differentiate the differences in suicidality intensity between patients (e.g., lower versus more severe suicidality), smaller sample size, and potential underreporting in claims data may explain the differences in results

between studies in relation to independent predictors of suicide ideation and suicide attempts.

IV. Objective 6

The aim of Objective 6 was to identify if post-index psychotic depression-related and all-cause health care utilization rates (i.e., hospitalizations, lengths of stay, and outpatient/emergency room visits) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates. For psychotic depression-related hospitalizations, approximately 3.9% and 0.4% had one hospitalization or two hospitalizations, respectively. For patients with at least one hospitalization, the mean (±SD) length of psychotic depression-related hospitalization stay was 7.3 (±3.8) days, where the overall mean (±SD) length of stay was 0.3 (±1.7) days. Approximately, 83.9% of the sample had at least one post-index outpatient/emergency department visit. About 22.1% of the sample had at least one all-cause hospitalization, and the corresponding mean (±SD) length of stay was 2.1 (±6.2) days. Almost the entire study sample (99.6%) had at least one all-cause outpatient/emergency department visit during the post-index period.

Primarily, previous studies involving MD-psy compared rates of health care utilization (e.g., hospitalization, length of stay, outpatient treatment, and emergency department visits) between psychotically depressed and non-psychotically depressed patients found higher rates of hospitalization and longer lengths of stay associated with patients with psychotic depression.[5,6,14,18-20] Out of 1,112 patients, Gaudiano and

associates[6] found that 15.0% (n=15 of 60) and 26.5% (n=17 of 60) of their sample of psychotically depressed patients had one or two previous psychiatric-related hospitalizations in their lifetime, respectively. Johnson and associates[5] conducted a large epidemiological study and reported a similar finding of 22.8% (n=26 of 114) for having at least one lifetime psychiatric hospitalization, and Forty and associates[20] reported an even higher rate of psychiatric hospital admission in 60.9% (n=39 of 64) of their psychotically depressed patients in their community-based study of 585 patients with major depressive disorder. Buoli and associates reported a mean (±SD) of 3.5 (±3.9) previous hospitalizations in their sample of 36 patients with psychotic depression. The rates of and average number of hospitalizations in previous studies are higher due to the present study's inability to conduct patient interviews and determine lifetime rates of hospitalization. Conversely, no patients reported new psychiatric hospitalizations at one year follow-up in the study by Johnson and associates,[5] where the low rate of re-hospitalization could be attributed to the smaller sample size compared to the present study (92 versus 926 patients).

Inpatient studies involving patients with psychotic depression estimated mean (±SD) lengths of psychiatric hospitalization stay that ranged from 19.0 (±10.2) days to 31.9 (±17.2) days.[14,18,19] Crebbin and associates[4] counted a total of 10,025 inpatient days over a thirteen year period for 81 patients with first-episode psychotic depression, where the mean length of stay was 95 days. Longer lengths of stay in previous studies could be attributed to differences in inpatient treatment practices across European countries and changes in treatment practices overtime in the US health care system (1990 versus 2010).

Johnson and associates[5] assessed psychiatric-related emergency department and outpatient visits in patients with psychotic depression and found that 15.1% had at least one emotional or drug-related emergency department visit, and 16.7%, 24.1% and 30.6% sought psychiatric outpatient treatment with an MD, psychiatrist, or both, respectively. Compared to the present study, the lower rates of outpatient and emergency department visits could be attributed to the lower sample size (n=114) and differences in socio-demographics (where 60.7% of the sample was of Caucasian race and only 20.7% of the sample was in the bottom quartile for socioeconomic status).

Only one study[5] focusing on psychotic depression estimated rates for all-cause hospitalizations (23.7%) and all-cause outpatient treatment (72.3%), and these results were similar to the findings of the present study. Also, two studies[21,22] that assessed adjunctive treatment with second-generation antipsychotics in patients with major depressive disorder (but not psychotic depression specifically) reported similar rates of all-cause hospitalization in patients taking combination therapy with aripiprazole (13.7% to 15.1%), olanzapine (22.7% to 23.3%), and quetiapine (23.1% to 27.7%). While the present study did not assess differences in rates within cohorts, the overall all-cause utilization rate was similar.

Finally, the present study adds to the literature by identifying significant factors associated with health care utilization (hospitalizations, length of stay, and outpatient/emergency department visits) in patients with major depression with psychotic features. Interestingly, those with tobacco use and/or dependence had significantly more all-cause outpatient/emergency department visits, compared to non-tobacco users

($p<0.05$). This finding may support the need for more research concerning the role of tobacco use and smoking in health care utilization in patients with mental health disorders.

V. Objective 7

The aim of Objective 7 was to determine if post-index psychotic depression-related and all-cause adjusted health care costs (i.e., medication, medical, and total costs) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates. Overall, the mean (±SD) costs for psychotic depression-related medication, medical and total costs were $1,717.53 (±2,532.07), $954.39 (±2,666.17), $2671.91 (±3,923.37), respectively. Significant predictors of higher total psychotic depression-related costs included: treatment cohort (AD/SGA), being male, not being African American, and increasing antidepressant persistence. In addition, the mean (±SD) costs for all-cause medication, medical and total costs were $3514.74 (±5,731.71), $17,761.92 (±36,304.30), $21,276.65 (±37,190.22), respectively. Significant predictors of higher total all-cause costs did not include treatment cohort, but did include: higher age, being female, being of Caucasian race, urban residence, higher Charlson Comorbidity Index score, and tobacco use and/or dependence.

Major depression studies[5,6] have determined that the societal costs associated with psychotic depression were significantly higher than the costs associated with depression without psychotic features ($p<0.05$). Psychotically depressed patients had higher rates of non-employment and receiving public assistance, welfare, and disability, compared to

patients with non-psychotic major depression ($p<0.05$). Interestingly, Leadholm and associates[15] found that receiving a disability pension was a significant protective factor against suicides in psychotic depressed patients. This is especially important since suicide attempts are associated with hospital admission and can potentially increase inpatient costs.[3,12]

While the present study did not focus on costs to society, direct costs to Texas Medicaid were evaluated. Only one psychotic depression-related study[4] estimated direct costs associated with psychotic depression. This study found that total psychiatric inpatient costs in Northern England were similar between patients with first-episode psychotic depression and patients with first-episode schizophrenia (£2.6 million versus £2.8 million, respectively) over a thirteen-year period. Two major depression cost studies[21,22] (which included patients with psychotic depression but did not evaluate psychotic depression separately) estimated the all-cause total medical costs associated with adjunctive treatment with aripiprazole, olanzapine, and quetiapine. Depending on the second-generation antipsychotic utilized, Halpern and associates[21] estimated all-cause medical costs to range from $10,664 to $16,556 over a 12-month period, where Nadkarni and associates[22] calculated all-cause medical costs to be in the range of $8,669 to $12,889. These reported costs are much lower than the mean all-cause medical cost of the present study, further emphasizing the detrimental role of psychotic depression (a more severe variant of major depressive disorder) in relation to health care expenditures. While previous psychotic depression studies did not assess predictors of health care costs, the

present study sheds some light on independent factors that may be important in MD-psy and should be further evaluated in future studies.

VI. Objectives 2 and 8

The aim of Objective 2 was to describe and compare the post-index cumulative incidence rates of dyslipidemia, diabetes mellitus, and extrapyramidal symptoms among cohorts. The aim of Objective 8 was to determine if the risks of medication therapy (incident dyslipidemia, incident diabetes mellitus, and incident extrapyramidal symptoms) differ between patients in the AD and AD/SGA cohorts, while controlling for covariates.

The overall cumulative incidence of dyslipidemia was 18.9% (n=134 of 709), where the rates for the AD cohort and AD/SGA cohort were 20.5% and 17.0%, respectively. A chi-square test (comparing incidence rates) and a Cox proportional hazards regression model (measuring survival time until the onset of dyslipidemia) found no significant differences between the two cohorts. While the majority studies in psychotic depression measured weight gain as the only metabolic adverse event,[11,23-27] a few studies assessed dyslipidemia in relation to changes in cholesterol, triglycerides, and lipids during pharmacological treatment.[7,26,28] Konstantinidis and associates[28] reported lower incidence rates of hyperlipidemia and hypercholesterolemia (both 4.0%), compared to the present study; however, their sample size was much smaller (n=25) and follow-up occurred after six weeks of combination therapy with citalopram and quetiapine. While Meyers and associates[7] of the STOP-PD study did not report new cases of dyslipidemia

after twelve weeks of use of olanzapine or olanzapine plus sertraline, the authors noted significant increases in triglycerides and cholesterol levels over time in both young and old patient groups. Correspondingly, age was found to be a significant predictor in the present study, where older age was associated with significantly higher hazards of progression to dyslipidemia. Deligiannidis and associates[26] also utilized data from the STOP-PD study and found that females had significantly higher total cholesterol and LDL levels, compared to males ($p<0.05$); however, no significant differences between treatments were observed.

The overall cumulative incidence of diabetes mellitus was 6.5% (n=49 of 750), where the rates for the AD cohort and the AD/SGA cohort were 6.8% and 6.3%, respectively. A chi-square test (comparing incidence rates) and a Cox proportional hazards regression model (measuring survival time until the onset of diabetes mellitus) found no significant differences between the two cohorts. While the majority studies in psychotic depression measured weight gain as the only metabolic adverse event,[11,23-27] Meyers and associates[7] of the STOP-PD study assessed changes in blood glucose levels after treatment with olanzapine or olanzapine plus sertraline and reported significantly higher levels of blood glucose in young patients at twelve weeks and/or study termination compared to baseline. While the effect of age was not assessed in the same way as the study above, age remained a significant positive predictor of progression to diabetes mellitus in the present study. Also, Deligiannidis and associates[26] also analyzed data from the STOP-PD study and found that younger patients had significantly lower levels of blood glucose, on average over the course of their visits, compared to older patients

($p<0.05$). This result parallels the present study, where increasing age is associated with higher hazards of the onset of diabetes mellitus.

The overall cumulative incidence of extrapyramidal symptoms was 1.3% (n=12 of 915), where the rates for the AD cohort and the AD/SGA cohort were 1.6% and 1.0%, respectively. A chi-square test comparing incidence rates of extrapyramidal symptoms found no significant difference between the two cohorts. Previous studies assessing the use of antidepressants and second-generation antipsychotics in psychotic depression reported much higher incidence rates of extrapyramidal symptoms (e.g., tremor, rigidity, akathisia, and tardive dyskinesia).[7,27-30] An eight-week open-label, naturalistic study reported an overall incidence rate of mild tremors in 3.9% (n=2 or 51) of patients who utilized combination therapy with an SGA (risperidone, olanzapine, or quetiapine) and an antidepressant (citalopram or venlafaxine). Also at the end of this study, one patient was switched from risperidone to quetiapine due to the onset of akathisia.[27] Meyers and associates[7] calculated incidence rates of 7.7% (n=20 of 259) and 8.5% (n=22 of 259) for akathisia and tardive dyskinesia, respectively, after twelve weeks of treatment with olanzapine and sertraline or olanzapine alone. A six-week study using combination therapy with quetiapine and citalopram reported a lower incidence rate for tremors at 4.0% (n=1 or 25),[28] and a five-week study utilizing combination therapy with citalopram and amisulpride led to tremors in 9.1% of patients (n=1 of 11).[29] Comparatively, Mulsant and associates[30] reported even higher rates of akathisia (25.0%) and tardive dyskinesia (18.8%) in their antidepressant cohort (nortriptyline); however, this study utilized a small sample (n=16) of older patients that were 50 years of age or older. Differences between

the present study's extrapyramidal symptom incidence rates and the existing literature are primarily associated with differences in study designs: prospective versus retrospective analyses, the use of placebos and randomization, and the use of clinical patient interviews. Also, very importantly, the use of Texas Medicaid retrospective claims data might not capture all cases of extrapyramidal symptoms that occurred during the study period; therefore, the incidence of extrapyramidal symptoms may be underreported.

STUDY LIMITATIONS AND FUTURE RESEARCH

To our knowledge, the present study is the first to analyze psychotic depression in relation to medication adherence, persistence, suicidality, health care utilization, health care costs, and medication safety among two different cohorts (antidepressant monotherapy versus combination therapy) of Texas Medicaid patients. While it utilizes several novel methodological approaches for the study of psychotic depression (i.e., MPR, PDC, persistence, place of residence, Charlson Comorbidity Index, and tobacco use and/or dependence), there are several limitations that must be addressed prior to interpreting the study results.

In general, the use of administrative claims data is associated with some limitations in itself. Firstly, the data only represent prescription claims—they are not necessarily indicative of actual prescription usage. However, this limitation was partially reduced by including only the patients that had at least two prescription claims—a proxy for medication usage. Secondly, claims data does not always allow researchers to ascertain the reasons why medications were prescribed (e.g., metformin prescribed for

diabetes versus weight loss). Thirdly, certain outcomes, such as tobacco use and/or dependence, suicidality, and medication adverse events are likely to be underreported in large claims databases. Fourthly, fraudulent claims and human error with miscoding could have occurred in these datasets. Fifthly, due to the limited patient database, the final sample size was smaller than anticipated, which may have led to decreased power especially when analyzing suicides attempts, suicide ideation, and medication adverse events. Finally, the study's generalizability is limited to populations similar to the original dataset – in this case, Texas Medicaid patients (e.g., indigent samples with high rates of African Americans and Hispanics) who were first-time users of antidepressant therapy for psychotic depression.

Selection bias was a substantial limitation in this study, where unmeasured patient factors might have unknowingly influenced the study outcomes. Because randomization was not utilized in this study, an equal distribution of all patient-related factors could not be assumed among cohorts. First of all, mental health scores and relapse rates were not available through Texas Medicaid claims data, and as a result, the authors were not able to assess whether one cohort was more likely to consist of patients with a higher degree of depression or psychosis severity over the other. The practice of utilizing antidepressant monotherapy first for the "healthier" patients cannot be ruled out, especially in light of certain international guideline practices where monotherapy is acknowledged as an option;[31] therefore, the bias of comparing unequal cohorts could be likely in this study. Secondly, since variables describing physician prescribing behavior were not available, the effect of guideline adoption rates on study outcomes could not be assessed. It is

possible that the lack of guideline adoption could have contributed to the larger sample of antidepressant monotherapy users in this study,[32] especially since the American Psychiatric Association[33] and Harvard South Shore Program[34] guidelines were not available throughout the full study period. However, it is important to keep in mind that at least one major set of recommendations on psychotic depression, the Texas Medication Algorithm Project guidelines which advocate the use of combination therapy, was available since 1999.[10] Thirdly, patients with successful suicides were not captured in this study; therefore, the authors were unable to determine whether monotherapy or combination therapy was more efficacious in terms of decreasing the number of completed suicides in psychotic depression. Fourthly, it is widely accepted that a high rate of patients (36.6-59.0%) with major depressive disorder smoke, and many of these patients self-medicate with tobacco in order to relieve the psychological and physical symptoms of depression.[35] Potentially, self-medication with tobacco could be an unmeasured confounder on study outcomes, and the possibility of decreased rates of antidepressant utilization, adherence, and persistence may unknowingly result. Finally, the study included patients with only one diagnosis for major depressive disorder with psychotic features. Future studies may decide to include patients with at least two diagnoses codes in order to exclude patients whose providers are ruling out psychotic depression. Overall, selection bias is problematic in this study as outcomes may be possibly due to inherent differences among patients versus the type of medication therapy received.

Other study limitations were associated with the inability to analyze the effect of: 1) individual second-generation antipsychotic agents, 2) individual antidepressant treatment, 3) smoking and medication dosages, 4) cognitive behavioral therapies, 5) electroconvulsive therapy, and 6) prescribing behaviors. Nevertheless, these limitations offer opportunities for future research in psychotic depression.

In the present study, aripiprazole, risperidone, and quetiapine were the top three second-generation antipsychotics utilized. Future studies could analyze differences between these second-generation antipsychotics (in addition to olanzapine) to determine which medication is associated with better health outcomes. Similarly, comparisons between tricyclic antidepressants (the most recommended antidepressants in treatment guidelines) and selective serotonin reuptake inhibitors (the most commonly used antidepressants in the present study) could be assessed. Other therapies such as cognitive behavioral and electroconvulsive therapy are utilized in the treatment of psychotic depression and ought to be studied further. Moreover, clinician behavior in relation to why one therapy is prescribed over another (i.e., antidepressant monotherapy versus combination therapy) and treatment guideline adherence could be examined in future studies. Finally, future studies which have access to more complete patient data could replicate the methodology of the present study with the addition of more clinical data, such as patient histories, relapses, depression scores, and psychosis scores. Further assessment of important factors on study outcomes (e.g., tobacco use and/or dependence) should also be considered in future studies on psychotic depression.

CONCLUSIONS AND IMPLICATIONS

In summary, the primary purpose of the present study was to analyze health-related outcomes of adherence, persistence, suicidality, health care utilization, health care costs, and medication safety associated with the treatment of psychotic depression. The results indicate that AD/SGA therapy users fared significantly better than AD monotherapy users in relation to antidepressant medication adherence based on MPR and PDC. Also, combination therapy users had significantly better antidepressant persistence rates based on a 45-day permissible gap and secondary analyses using 30-day and 60-day gaps. Alternatively, AD monotherapy users had a significantly lower rate of psychotic depression-related outpatient/emergency department visits, as well as significantly lower psychotic depression-related costs for medication, medical, and total costs and all-cause medication costs.

The implications of the study results are generally positive. First of all, the present study adds to the existing literature on psychotic depression and has filled a gap in knowledge related to medication adherence, persistence, health care utilization and costs for Texas Medicaid patients with psychotic depression. Secondly, the study results might have an impact on treatment decisions, especially for Texas Medicaid beneficiaries and the clinicians serving Texas Medicaid patients. While this study does not have the ability to interpret which therapy is more efficacious over the other, the results support that increased medication utilization leads to increased rates of medical care and costs. Texas Medicaid decision makers may need to conduct more studies on psychotic depression in

order to further delineate when one therapy may be appropriate over the other in terms of treatment efficacy and decreasing health care waste. Research assessing treatment non-adherence in patients and treatment guideline non-adherence in clinicians could also be further investigated by Texas Medicaid decision makers. Overall, the authors support the need for research and interventions in order to reduce costs and improve outcomes in patients with psychotic depression. This study aimed to provide real-world estimates of psychotic depression-related outcomes, and the authors hope the study findings provide a positive step forward in understanding appropriate treatment for major depressive disorder with psychotic features.

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Vita

Dawn Kim-Romo was born in Austin, Texas. She obtained her Doctor of Pharmacy degree in May 2009 from The University of Texas at Austin in conjunction with The University of Texas Health Science Center in San Antonio. Upon graduation, Dr. Kim-Romo married the love of her life and fellow pharmacy school graduate, Dr. Anthony James Romo. After joining the Health Outcomes and Pharmacy Practice graduate program at The University of Texas at Austin in 2010, she went on to complete her Master's degree in Pharmacy in May 2012. In July 2013, Dr. Kim-Romo was awarded a prestigious two-year pre-doctoral fellowship in Health Outcomes from the Pharmaceutical Research and Manufacturers of America Foundation. During her last year of candidacy, Dr. Kim-Romo was blessed with her first child, Julian Anthony Romo.

Permanent email: dawnkim@utexas.edu

This dissertation was typed by Dawn Nicole Kim-Romo.